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P034644GB : CJM

2. Patent application number
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3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

CHIRON SRL
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Patents ADP number *(if you know it)*

86088120001

If the applicant is a corporate body, give the country/state of its incorporation

ITALY

4. Title of the invention

VIRULENCE-ASSOCIATED ADHESINS

5. Name of your agent *(if you have one)*

Carpmaels & Ransford

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

43 Bloomsbury Square
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WC1A 2RA

Patents ADP number *(if you know it)*

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Number of earlier application	Date of filing *(day / month / year)*

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Signature — Date

Carpmaels & Ransford — **26th June 2003**

12. Name and daytime telephone number of person to contact in the United Kingdom

Carpmaels & Ransford

CAMERON J. MARSHALL 020-7242 8692

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VIRULENCE-ASSOCIATED ADHESINS

All documents cited herein are incorporated by reference in their entirety.

TECHNICAL FIELD

This invention is in the field of bacterial adhesion. In particular, it relates to virulence-related adhesion antigens derived from *Haemophilus influenzae, Escherichia coli* and other organisms.

BACKGROUND ART

The Gram negative *Haemophilus* genus includes *H.influenzae, H.aegyptius* (also referred to as *H.influenzae* biogroup *aegyptius*), *H.decreyi* and *H.somnus*. These bacteria can cause diseases including conjunctivitis, chancroid, purpuric fever, meningitis, pneumonia and epiglottitis. *H.influenzae* is the most commonly-found pathogen in this genus, and includes both typeable (encapsulated) and non-typeable (non-capsulated; 'NTHi') strains.

A vaccine against *H.influenzae* type B ('Hib') based on a conjugate of its capsular saccharide and a carrier protein has been enormously successful, but there has been little progress in providing protection against other members of the species. In particular, type D *H.influenzae* and non-typeable *H.influenzae* remain problematic.

Similarly, vaccines remain unavailable for other bacterial pathogens such as enterotoxigenic (ETEC), enteropathogenic (EPEC), enteroaggregative (EAEC), enterohemorrhagic (EHEC) and shiga-toxic (STEC) strains of *Escherichia coli*.

It is an object of the invention to provide materials and methods to improve the prevention and treatment of infections caused by such bacteria. More particularly, it is an object of the invention to provide materials suitable for immunising against bacterial infections.

DISCLOSURE OF THE INVENTION

Virulence-associated antigens involved in adhesion have been identified in several bacteria, and these antigens are useful for the diagnosis, prevention and treatment of bacterial infections (particularly those caused by virulent strains). In particular, antigens have been identified in: *Haemophilus influenzae* biogroup *aegyptius* (SEQ ID NO: 1); *Escherichia coli* K1 (SEQ ID NO^S: 2 & 3) and also in EHEC strain EDL933; *Actinobacillus actinomycetemcomitans* (SEQ ID NO: 4); *Haemophilus somnus* (SEQ ID NO: 5); *Haemophilus ducreyi* (SEQ ID NO: 6); EPEC *E.coli* strain E2348/69 (SEQ ID NO^S: 7 & 29); EAEC *E.coli* strain O42 (SEQ ID NO^S: 8 & 9); uropathogenic *E.coli* (SEQ ID NO: 10); *Shigella flexneri* (SEQ ID NO: 11); *Brucella melitensis* (SEQ ID NO: 12); *Brucella suis* (SEQ ID NO: 13); *Ralstonia solanacearum* (SEQ ID NO: 14); *Sinorhizobium meliloti* (SEQ ID NO: 15); *Bradorhizobium japonicum* (SEQ ID NO: 16); and *Burkholderia fungorum* (SEQ ID NO: 17).

Although the degree of sequence identity between the antigens of the invention is low, an appreciation of the antigens at a level beyond simple primary sequence information shows that they share a common arrangement of domains from N-terminus to C-terminus, namely:

- a leader peptide
- a globular head
- a coiled-coil region
- a transmembrane anchor region

Sequence similarity between the various antigens is largely restricted to the C-terminal anchor region. This arrangement of domains is shared with *N.meningitidis* protein NadA {1}.

The positions of these features in SEQ ID NO^{S}: 1 to 18 are as follows:

SEQ ID	Organism	Length	Leader	Head	Coiled-coil	Anchor
1	*H.aegyptius*	>223	1-26	27-55	56-184	185...
2	EHEC	338	1-23	24-207	208-266	267-338
3		1588	1-53	54-1515 *		1516-1588
4	*A.actinomycetemcomitans*	295	1-25	26-150	151-222	223-295
5	*H.somnus*	452	1-26	27-158	159-378	379-452
6	*H.ducreyi*	273	1-21	22-198 *		199-273
7	EPEC	338	1-24	25-209	210-266	267-338
8	EAEC	717	1-23	24-109	110-645	646-717
9		1743	1-53	54-1670 *		1671-1743
10	UPEC	1778	1-53	54-1705 *		1706-1778
11	*S.flexneri*	990	1-917 *			918-990
12	*B.melitensis*	227	1-27	28-122	123-154	155-227
13	*B.suis*	311	1-27	28-206	207-238	239-311
14	*R.solanacearum*	1309	1-230 *		231-708	1239-1309
15	*S.meliloti*	1291	1-1219 *			1220-1291
16	*B.japonicum*	372	1-72	73-300 *		301-372
17	*B.fungorum*	3399	1-57	58-3328 *		3329-3399
18	EPEC	577	1-504 *			505-577

* The boundary between domains is less distinct for some polypeptides of the invention

Antigens

The invention provides a polypeptide comprising one or more of the following amino acid sequences: SEQ ID NO^{S}: 1 to 18.

The invention also provides a polypeptide comprising an amino acid sequence: (a) having at least *m*% identity to one or more of SEQ ID NO^{S}: 1-18, where *m* is 50 or more (*e.g.* 60, 65, 70, 75, 80, 85, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 99.5 or more); and/or (b) which is a fragment of at least *n* consecutive amino acids of one or more of SEQ ID NO^{S}: 1-18, wherein *n* is 7 or more (*e.g.* 8, 10, 12,

, 16, 18, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100, 150, 200, 250 or more). These polypeptides include variants (*e.g.* allelic variants, homologs, orthologs, paralogs, mutants, *etc.*) of SEQ ID NO^S: 1-18.

Preferred fragments of (b) comprise an epitope from one or more of SEQ ID NO^S: 1-18, preferably a B-cell epitope. B-cell epitopes can be identified empirically or can be predicted algorithmically.

Other preferred fragments of (b) lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 45 or more) from the N-terminus of the relevant amino acid sequence from SEQ ID NO^S: 1-18. In particular, preferred fragments omit at least the N-terminus leader sequence.

Other preferred fragments omit one or more (*i.e.* 1, 2, or 3) of the four domains of SEQ ID NO^S: 1-18, based on the above table. Other preferred fragments consist of one or more (*i.e.* 1, 2, or 3) of the four domains of SEQ ID NO^S: 1-18.

Preferred polypeptides of the invention are presented in oligomeric form (*e.g.* dimers, trimers, tetramers, *etc.*). Trimers are preferred, but monomeric polypeptides of the invention are also useful.

The invention also provides polypeptides of the formula **NH_2-A-{-X-L-}$_x$-B-COOH**, wherein:

- X comprises an amino acid sequence: (a) having at least *m*% identity to one or more of SEQ ID NO^S: 1-18; and/or (b) which is a fragment of at least *n* consecutive amino acids of one or more of SEQ ID NO^S: 1-18, as defined above;
- L is an optional linker amino acid sequence;
- A is an optional N-terminal amino acid sequence;
- B is an optional C-terminal amino acid sequence; and
- *x* is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17 or 18 (preferably *x*=2).

Where a -X- moiety has a leader peptide, this may be included or omitted in the hybrid protein. In some embodiments, the leader peptides will be deleted except for that of the -X- moiety located at the N-terminus of the hybrid protein *i.e.* the leader peptide of X_1 will be retained, but the leader peptides of X_2 ... X_x will be omitted. This is equivalent to deleting all leader peptides and using the leader peptide of X_1 as moiety -A-.

For each *x* instances of {-X-L-}, -X- may be the same or different, and linker amino acid sequence -L- may be present or absent. For instance, when *x*=2 the hybrid may be NH_2-X_1-L_1-X_2-L_2-COOH, NH_2-X_1-X_2-COOH, NH_2-X_1-L_1-X_2-COOH, NH_2-X_1-X_2-L_2-COOH, *etc.* Linker amino acid sequence(s) -L- will typically be short (*e.g.* 20 or fewer amino acids *i.e.* 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, 1). Examples comprise short peptide sequences which facilitate cloning, poly-glycine linkers (*i.e.* comprising Gly_n where n = 2, 3, 4, 5, 6, 7, 8, 9, 10 or more), and histidine tags (*i.e.* His_n where n = 3, 4, 5, 6, 7, 8, 9, 10 or more). Other suitable linker amino acid sequences

ill be apparent to those skilled in the art. A useful linker is GSGGGG (SEQ ID NO: 19), with the Gly-Ser dipeptide being formed from a *Bam*HI restriction site, thus aiding cloning and manipulation, and the $(Gly)_4$ tetrapeptide being a typical poly-glycine linker.

-A- is an optional N-terminal amino acid sequence. This will typically be short (*e.g.* 40 or fewer amino acids *i.e.* 39, 38, 37, 36, 35, 34, 33, 32, 31, 30, 29, 28, 27, 26, 25, 24, 23, 22, 21, 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, 1). Examples include leader sequences to direct protein trafficking, or short peptide sequences which facilitate cloning or purification (*e.g.* histidine tags *i.e.* His_h where h = 3, 4, 5, 6, 7, 8, 9, 10 or more). Other suitable N-terminal amino acid sequences will be apparent to those skilled in the art. If X_1 lacks its own N-terminus methionine, -A- is preferably an oligopeptide (*e.g.* with 1, 2, 3, 4, 5, 6, 7 or 8 amino acids) which provides a N-terminus methionine.

-B- is an optional C-terminal amino acid sequence. This will typically be short (*e.g.* 40 or fewer amino acids *i.e.* 39, 38, 37, 36, 35, 34, 33, 32, 31, 30, 29, 28, 27, 26, 25, 24, 23, 22, 21, 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, 1). Examples include sequences to direct protein trafficking, short peptide sequences which facilitate cloning or purification (*e.g.* comprising histidine tags *i.e.* His_h where h = 3, 4, 5, 6, 7, 8, 9, 10 or more), or sequences which enhance protein stability. Other suitable C-terminal amino acid sequences will be apparent to those skilled in the art.

The invention also provides polypeptides comprising the amino acid sequence:

-A-W_1-W_2-W_3-W_4-B-

wherein:

- A is an optional sequence as defined above (preferably at the N-terminus of the polypeptide);
- B is an optional sequence as defined above (preferably at the C-terminus of the polypeptide);
- W_1 is an optional amino acid sequence: (a) having at least m% identity to the leader peptide of one or more of SEQ ID NO^S: 1-18; and/or (b) which is a fragment of at least n consecutive amino acids of the leader peptide of one or more of SEQ ID NO^S: 1-18;
- W_2 is an optional amino acid sequence: (a) having at least m% identity to the globular head domain of one or more of SEQ ID NO^S: 1-18; and/or (b) which is a fragment of at least n consecutive amino acids of the globular head domain of one or more of SEQ ID NO^S: 1-18;
- W_3 is an optional amino acid sequence: (a) having at least m% identity to the coiled-coil domain of one or more of SEQ ID NO^S: 1-18; and/or (b) which is a fragment of at least n consecutive amino acids of the coiled-coil domain of one or more of SEQ ID NO^S: 1-18;
- W_4 is an optional amino acid sequence: (a) having at least m% identity to the transmembrane anchor region of one or more of SEQ ID NO^S: 1-18; and/or (b) which is a fragment of at least n consecutive amino acids of the transmembrane anchor region of one or more of SEQ ID NO^S: 1-18;

provided that at least one of W_1, W_2, W_3 or W_4 is present.

The invention also provides a polypeptide comprising a polypeptide as described above, wherein the amino acid sequence of the polypeptide contains one or more amino acid mutations. The mutation(s) preferably result in the reduction or removal of an activity of a polypeptide of the invention which is responsible directly or indirectly for virulence or adhesion. For example, the mutation may inhibit an enzymatic activity or may remove a binding site in the protein. Mutation may involve deletion, substitution, and/or insertion, any of which may be involve one or more amino acids. As an alternative, the mutation may involve truncation.

Mutagenesis of virulence factors is a well-established science for many bacteria {*e.g.* toxin mutagenesis described in refs. 2 to 8}. Mutagenesis may be specifically targeted to nucleic acid encoding a polypeptide of the invention. Alternatively, mutagenesis may be global or random (*e.g.* by irradiation, chemical mutagenesis, *etc.*), which will typically be followed by screening bacteria for those in which a mutation has been introduced into a gene encoding a polypeptide of the invention. Such screening may be by hybridisation assays (*e.g.* Southern or Northern blots *etc.*), primer-based amplification (*e.g.* PCR), sequencing, proteomics, aberrant SDS-PAGE gel migration, *etc.*

Polypeptides of the invention can be prepared by various means (*e.g.* recombinant expression, purification from cell culture, chemical synthesis, *etc.*) and in various forms (*e.g.* native, fusions, non-glycosylated, lipidated, *etc.*). They are preferably prepared in substantially pure form (*i.e.* substantially free from other bacterial or host cell proteins).

Whilst expression of the polypeptides of the invention may take place in the native host, the invention preferably utilises a heterologous host. The heterologous host may be prokaryotic (*e.g.* a bacterium) or eukaryotic. It is preferably *E.coli*, but other suitable hosts include *Bacillus subtilis, Vibrio cholerae, Salmonella typhi, Salmonella typhimurium, Neisseria lactamica, Neisseria cinerea, Mycobacteria* (*e.g. M.tuberculosis*), yeasts, *etc.*

Antibodies

The invention also provides antibodies which bind to polypeptides of the invention.

Antibody of the invention preferably has an affinity for a polypeptide of the invention of at least 10^{-7} M *e.g.* 10^{-8} M, 10^{-9} M, 10^{-10} M or tighter. Preferred antibodies can block the ability of a polypeptide of the invention to bind to a human cell.

Antibodies of the invention may be polyclonal or monoclonal and may be produced by any suitable means (*e.g.* by recombinant expression, purification from cell culture, chemical synthesis, *etc.*) and in various forms (*e.g.* native, fusions, glycosylated, non-glycosylated, *etc.*). They are preferably prepared in substantially pure form (*i.e.* substantially free from other antibodies).

The term "antibody" includes whole antibodies, Fv, scFv, Fc, Fab, $F(ab')_2$, *etc.*

Antibodies of the invention may include a label. The label may be detectable directly, such as a radioactive or fluorescent label. Alternatively, the label may be detectable indirectly, such as an enzyme whose products are detectable (*e.g.* luciferase, β-galactosidase, peroxidase, *etc.*).

Antibodies of the invention may be attached to a solid support.

Antibodies of the invention may be prepared by administering (*e.g.* injecting) a polypeptide of the invention to an appropriate animal (*e.g.* a rabbit, hamster, mouse or other rodent).

To increase compatibility with the human immune system, the antibodies may be chimeric or humanized {*e.g.* refs. 9 & 10}, or fully human antibodies may be used. Because humanized antibodies are far less immunogenic in humans than the original non-human monoclonal antibodies, they can be used for the treatment of humans with far less risk of anaphylaxis. Thus, these antibodies may be preferred in therapeutic applications that involve *in vivo* administration to a human such as, use as radiation sensitizers for the treatment of neoplastic disease or use in methods to reduce the side effects of cancer therapy.

Humanized antibodies may be achieved by a variety of methods including, for example: (1) grafting non-human complementarity determining regions (CDRs) onto a human framework and constant region ("humanizing"), with the optional transfer of one or more framework residues from the non-human antibody; (2) transplanting entire non-human variable domains, but "cloaking" them with a human-like surface by replacement of surface residues ("veneering"). In the present invention, humanized antibodies will include both "humanized" and "veneered" antibodies. {11, 12, 13, 14, 15, 16, 17}. Humanized or fully-human antibodies can also be produced using transgenic animals that are engineered to contain human immunoglobulin loci.

The phrase "constant region" refers to the portion of the antibody molecule that confers effector functions. In chimeric antibodies, mouse constant regions are substituted by human constant regions. The constant regions of humanized antibodies are derived from human immunoglobulins. The heavy chain constant region can be selected from any of the 5 isotypes: alpha, delta, epsilon, gamma or mu.

Nucleic acids

The invention also provides nucleic acid encoding the polypeptides of the invention. Furthermore, the invention provides nucleic acid which can hybridise to this nucleic acid, preferably under "high stringency" conditions (*e.g.* 65°C in a 0.1xSSC, 0.5% SDS solution).

Nucleic acid according to the invention can be prepared in many ways (*e.g.* by chemical synthesis, from genomic or cDNA libraries, from the organism itself, *etc.*) and can take various forms (*e.g.* single stranded, double stranded, vectors, probes, *etc.*). They are preferably prepared in substantially pure form (*i.e.* substantially free from other bacterial or host cell nucleic acids).

e term "nucleic acid" includes DNA and RNA, and also their analogues, such as those containing modified backbones (*e.g.* phosphorothioates, *etc.*), and also peptide nucleic acids (PNA), *etc.* The invention includes nucleic acid comprising sequences complementary to those described above (*e.g.* for antisense or probing purposes).

Immunogenic compositions and medicaments

Based on the structural and functional similarities to NadA, which is a good anti-meningococcal immunogen {1}, including their association with virulence, the polypeptides of the invention should also be useful for immunisation purposes.

The invention provides a composition comprising a polypeptide and/or a nucleic acid and/or an antibody of the invention. Compositions of the invention are preferably immunogenic compositions, and are more preferably vaccine compositions. Vaccines according to the invention may either be prophylactic (*i.e.* to prevent infection) or therapeutic (*i.e.* to treat infection), but will typically be prophylactic.

The pH of the composition is preferably between 6 and 8, preferably about 7. The pH may be maintained by the use of a buffer. The composition may be sterile and/or pyrogen-free. The composition may be isotonic with respect to humans.

The invention also provides a composition of the invention for use as a medicament. The medicament is preferably able to raise an immune response in a mammal (*i.e.* it is an immunogenic composition) and is more preferably a vaccine.

The invention also provides the use of one or more (*e.g.* 2, 3, 4, 5, 6) of the polypeptides of the invention in the manufacture of a medicament for raising an immune response in a mammal. The medicament is preferably a vaccine.

The invention also provides a method for raising an immune response in a mammal comprising the step of administering an effective amount of a composition of the invention. The immune response is preferably protective and preferably involves antibodies and/or cell-mediated immunity. The method may raise a booster response.

The mammal is preferably a human. Where the vaccine is for prophylactic use, the human is preferably a child (*e.g.* a toddler or infant) or a teenager; where the vaccine is for therapeutic use, the human is preferably a teenager or an adult. A vaccine intended for children may also be administered to adults *e.g.* to assess safety, dosage, immunogenicity, *etc.*

These uses and methods are preferably for the prevention and/or treatment of a disease caused by *Haemophilus influenzae* biogroup *aegyptius, Escherichia coli* (particularly EHEC, EAEC, ETEC, EPEC and UPEC strains), *Actinobacillus actinomycetemcomitans, Haemophilus somnus, Haemophilus ducreyi, Shigella flexneri, Brucella melitensis, Brucella suis, Ralstonia solanacearum,*

orhizobium meliloti, Bradorhizobium japonicum and *Burkholderia fungorum*. Thus the invention is suitable for the prevention and/or treatment of diseases including: conjunctivitis, chancroid, purpuric fever, meningitis, pneumonia, epiglottitis, peri-implantitis, periodontal disease, gingivitis, bovine encephalitis, arthritis, myocarditis, diarrhoea, ovine abortion, orchitis, undulant fever, porcine reproductive wastage, brucellosis, *etc.*

One way of checking efficacy of therapeutic treatment involves monitoring bacterial infection after administration of the composition of the invention. One way of checking efficacy of prophylactic treatment involves monitoring immune responses against the polypeptides after administration of the composition.

Compositions of the invention will generally be administered directly to a patient. Direct delivery may be accomplished by parenteral injection (*e.g.* subcutaneously, intraperitoneally, intravenously, intramuscularly, or to the interstitial space of a tissue), or by rectal, oral (*e.g.* tablet, spray), vaginal, topical, transdermal {*e.g.* see ref. 18} or transcutaneous {*e.g.* see refs. 19 & 20}, intranasal {*e.g.* see ref. 21}, ocular, aural, pulmonary or other mucosal administration.

The invention may be used to elicit systemic and/or mucosal immunity.

Dosage treatment can be a single dose schedule or a multiple dose schedule. Multiple doses may be used in a primary immunisation schedule and/or in a booster immunisation schedule. In a multiple dose schedule the various doses may be given by the same or different routes *e.g.* a parenteral prime and mucosal boost, a mucosal prime and parenteral boost, *etc.*

Bacterial infections affect various areas of the body and so the compositions of the invention may be prepared in various forms. For example, the compositions may be prepared as injectables, either as liquid solutions or suspensions. Solid forms suitable for solution in, or suspension in, liquid vehicles prior to injection can also be prepared (*e.g.* a lyophilised composition). The composition may be prepared for topical administration *e.g.* as an ointment, cream or powder. The composition may be prepared for oral administration *e.g.* as a tablet or capsule, as a spray, or as a syrup (optionally flavoured). The composition may be prepared for pulmonary administration *e.g.* as an inhaler, using a fine powder or a spray. The composition may be prepared as a suppository or pessary. The composition may be prepared for nasal, aural or ocular administration *e.g.* as drops. The composition may be in kit form, designed such that a combined composition is reconstituted just prior to administration to a patient. Such kits may comprise one or more antigens in liquid form and one or more lyophilised antigens.

Immunogenic compositions used as vaccines comprise an immunologically effective amount of antigen(s), as well as any other components, as needed. By 'immunologically effective amount', it is meant that the administration of that amount to an individual, either in a single dose or as part of a series, is effective for treatment or prevention. This amount varies depending upon the health and

ysical condition of the individual to be treated, age, the taxonomic group of individual to be treated (*e.g.* non-human primate, primate, *etc.*), the capacity of the individual's immune system to synthesise antibodies, the degree of protection desired, the formulation of the vaccine, the treating doctor's assessment of the medical situation, and other relevant factors. It is expected that the amount will fall in a relatively broad range that can be determined through routine trials.

The invention also provides the polypeptides of the invention (including NadA itself) for use as adjuvants (parenteral and/or mucosal). Similarly, the invention provides a composition comprising a polypeptide of the invention in admixture with a second antigen, whereby the polypeptide of the invention enhances the immune response against the second antigen when administered to a patient.

Further components of the composition

The composition of the invention will typically, in addition to the components mentioned above, comprise one or more 'pharmaceutically acceptable carriers', which include any carrier that does not itself induce the production of antibodies harmful to the individual receiving the composition. Suitable carriers are typically large, slowly metabolised macromolecules such as proteins, polysaccharides, polylactic acids, polyglycolic acids, polymeric amino acids, amino acid copolymers, and lipid aggregates (such as oil droplets or liposomes). Such carriers are well known to those of ordinary skill in the art. The vaccines may also contain diluents, such as water, saline, glycerol, *etc.* Additionally, auxiliary substances, such as wetting or emulsifying agents, pH buffering substances, and the like, may be present. A thorough discussion of pharmaceutically acceptable excipients is available in reference 22.

Vaccines of the invention may be administered in conjunction with other immunoregulatory agents. In particular, compositions will usually include an adjuvant. Preferred further adjuvants include, but are not limited to: (A) aluminium salts, including hydroxides (*e.g.* oxyhydroxides), phosphates (*e.g.* hydroxyphoshpates, orthophosphates), sulphates, *etc.* {*e.g.* see chapters 8 & 9 of ref. 23}), or mixtures of different aluminium compounds, with the compounds taking any suitable form (*e.g.* gel, crystalline, amorphous, *etc.*), and with adsorption being preferred; (B) MF59 (5% Squalene, 0.5% Tween 80, and 0.5% Span 85, formulated into submicron particles using a microfluidizer) {see Chapter 10 of 23; see also ref. 24}; (C) liposomes {see Chapters 13 and 14 of ref. 23}; (D) ISCOMs {see Chapter 23 of ref. 23}, which may be devoid of additional detergent {25}; (E) SAF, containing 10% Squalane, 0.4% Tween 80, 5% pluronic-block polymer L121, and thr-MDP, either microfluidized into a submicron emulsion or vortexed to generate a larger particle size emulsion {see Chapter 12 of ref. 23}; (F) Ribi™ adjuvant system (RAS), (Ribi Immunochem) containing 2% Squalene, 0.2% Tween 80, and one or more bacterial cell wall components from the group consisting of monophosphorylipid A (MPL), trehalose dimycolate (TDM), and cell wall skeleton (CWS), preferably MPL + CWS (Detox™); (G) saponin adjuvants, such as QuilA or QS21 {see Chapter 22 of ref. 23}, also known as Stimulon™ {26}; (H) chitosan {*e.g.* 27}; (I) complete Freund's adjuvant (CFA) and incomplete Freund's adjuvant (IFA); (J) cytokines, such as interleukins (*e.g.* IL-1, IL-2,

-4, IL-5, IL-6, IL-7, IL-12, *etc.*), interferons (*e.g.* interferon-γ), macrophage colony stimulating factor, tumor necrosis factor, *etc.* {see Chapters 27 & 28 of ref. 23}; (K) monophosphoryl lipid A (MPL) or 3-O-deacylated MPL (3dMPL) {*e.g.* chapter 21 of ref. 23}; (L) combinations of 3dMPL with, for example, QS21 and/or oil-in-water emulsions {28}; (M) a polyoxyethylene ether or a polyoxyethylene ester {29}; (N) a polyoxyethylene sorbitan ester surfactant in combination with an octoxynol {30} or a polyoxyethylene alkyl ether or ester surfactant in combination with at least one additional non-ionic surfactant such as an octoxynol {31}; (N) a particle of metal salt {32}; (O) a saponin and an oil-in-water emulsion {33}; (P) a saponin (*e.g.* QS21) + 3dMPL + IL-12 (optionally + a sterol) {34}; (Q) *E.coli* heat-labile enterotoxin ("LT"), or detoxified mutants thereof, such as the K63 or R72 mutants {*e.g.* Chapter 5 of ref. 35}; (R) cholera toxin ("CT"), or detoxified mutants thereof {*e.g.* Chapter 5 of ref. 35}; (S) double-stranded RNA; (T) microparticles (*i.e.* a particle of ~100nm to ~150μm in diameter, more preferably ~200nm to ~30μm in diameter, and most preferably ~500nm to ~10μm in diameter) formed from materials that are biodegradable and non-toxic (*e.g.* a poly(α-hydroxy acid), a polyhydroxybutyric acid, a polyorthoester, a polyanhydride, a polycaprolactone, *etc.*), with poly(lactide-co-glycolide) being preferred, optionally treated to have a negatively-charged surface (*e.g.* with SDS) or a positively-charged surface (*e.g.* with a cationic detergent, such as CTAB); (U) oligonucleotides comprising CpG motifs *i.e.* containing at least one CG dinucleotide, with 5-methylcytosine optionally being used in place of cytosine; (V) monophosphoryl lipid A mimics, such as aminoalkyl glucosaminide phosphate derivatives *e.g.* RC-529 {36}; (W) polyphosphazene (PCPP); (X) a bioadhesive {37} such as esterified hyaluronic acid microspheres {38} or a mucoadhesive selected from the group consisting of cross-linked derivatives of poly(acrylic acid), polyvinyl alcohol, polyvinyl pyrollidone, polysaccharides and carboxymethylcellulose; or (Y) other substances that act as immunostimulating agents to enhance the effectiveness of the composition {*e.g.* see Chapter 7 of ref. 23}. Aluminium salts and MF59 are preferred adjuvants for parenteral immunisation. Mutant toxins are preferred mucosal adjuvants.

Muramyl peptides include N-acetyl-muramyl-L-threonyl-D-isoglutamine (thr-MDP), N-acetyl-normuramyl-L-alanyl-D-isoglutamine (nor-MDP), N-acetylmuramyl-L-alanyl-D-isoglutaminyl-L-alanine-2-(1'-2'-dipalmitoyl-*sn*-glycero-3-hydroxyphosphoryloxy)-ethylamine MTP-PE), *etc.*

The composition may include an antibiotic.

Further antigens

As well as containing polypeptides of the invention, the compositions of the invention may also include one or more further antigens. Further antigens for inclusion may be, for example:

- a saccharide antigen from *N.meningitidis* serogroup A, C, W135 and/or Y, such as the oligosaccharide disclosed in ref. 39 from serogroup C {see also ref. 40} or the oligosaccharides of ref. 41.
- antigens from *Helicobacter pylori* such as CagA {42 to 45}, VacA {46, 47}, NAP {48, 49, 50}, HopX {*e.g.* 51}, HopY {*e.g.* 51} and/or urease.
- a saccharide antigen from *Streptococcus pneumoniae* {*e.g.* 52, 53, 54}.

- a protein antigen from *Streptococcus pneumoniae* {*e.g.* 55}.
- an antigen from hepatitis A virus, such as inactivated virus {*e.g.* 56, 57}.
- an antigen from hepatitis B virus, such as the surface and/or core antigens {*e.g.* 57, 58}.
- an antigen from hepatitis C virus {*e.g.* 59}.
- a diphtheria antigen, such as a diphtheria toxoid {*e.g.* chapter 3 of ref. 60} *e.g.* the CRM_{197} mutant {*e.g.* 61}.
- a tetanus antigen, such as a tetanus toxoid {*e.g.* chapter 4 of ref. 60}.
- an antigen from *Bordetella pertussis*, such as pertussis holotoxin (PT) and filamentous haemagglutinin (FHA) from *B.pertussis*, optionally also in combination with pertactin and/or agglutinogens 2 and 3 {*e.g.* refs. 62 & 63}; whole-cell pertussis antigen may also be used.
- a saccharide antigen from *Haemophilus influenzae* B {*e.g.* 40}.
- polio antigen(s) {*e.g.* 64, 65} such as OPV or, preferably, IPV.
- a protein antigen from *N.meningitidis* serogroup B {*e.g.* refs. 66 to 77}, such as NadA.
- an outer-membrane vesicle (OMV) preparation from *N.meningitidis* serogroup B, such as those disclosed in refs. 78, 79, 80, 81, *etc.*
- an antigen from *Chlamydia pneumoniae* {*e.g.* refs. 82 to 88}.
- an antigen from *Chlamydia trachomatis* {*e.g.* 89}.
- an antigen from *Porphyromonas gingivalis* {*e.g.* 90}.
- rabies antigen(s) {*e.g.* 91} such as lyophilised inactivated virus {*e.g.* 92, RabAvert™}.
- measles, mumps and/or rubella antigens {*e.g.* chapters 9, 10 & 11 of ref. 60}.
- influenza antigen(s) {*e.g.* chapter 19 of ref. 60}, such as the hemagglutinin and/or neuraminidase surface proteins.
- an antigen from *N.gonorrhoeae* {*e.g.* 93, 94, 95, 96}.
- antigen(s) from a paramyxovirus such as respiratory syncytial virus (RSV {97, 98}) and/or parainfluenza virus (PIV3 {99}).
- an antigen from *Moraxella catarrhalis* {*e.g.* 100}, such as UspA1 and/or UspA2
- an antigen from *Streptococcus pyogenes* (group A streptococcus) {*e.g.* 101, 102, 103}.
- an antigen from *Streptococcus agalactiae* (group B streptococcus) {*e.g.* 104}.
- an antigen from *Staphylococcus aureus* {*e.g.* 105}.
- an antigen from *Bacillus anthracis* {*e.g.* 106, 107, 108}.
- an antigen from a virus in the flaviviridae family (genus flavivirus), such as from yellow fever virus, Japanese encephalitis virus, four serotypes of Dengue viruses, tick-borne encephalitis virus, West Nile virus.
- an antigen from *Pseudomonas*.
- an antigen from a HIV *e.g.* a HIV-1 or HIV-2.
- an antigen from a rotavirus.

- a pestivirus antigen, such as from classical porcine fever virus, bovine viral diarrhoea virus, and/or border disease virus.
- a parvovirus antigen *e.g.* from parvovirus B19.
- a coronavirus antigen *e.g.* from the SARS coronoavirus.
- a cancer antigen, such as those listed in Table 1 of ref. 109 or in tables 3 & 4 of ref. 110.

The composition may comprise one or more of these further antigens. It is preferred that combinations of antigens should be based on shared characteristics *e.g.* antigens associated with respiratory diseases, antigens associated with enteric diseases, antigens associated with sexually-transmitted diseases, *etc.*

Where a saccharide or carbohydrate antigen is used, it is preferably conjugated to a carrier protein in order to enhance immunogenicity {*e.g.* refs. 111 to 120}. Preferred carrier proteins are bacterial toxins or toxoids, such as diphtheria or tetanus toxoids. The CRM_{197} diphtheria toxoid is particularly preferred {121}. Other carrier polypeptides include the *N.meningitidis* outer membrane protein {122}, synthetic peptides {123, 124}, heat shock proteins {125, 126}, pertussis proteins {127, 128}, protein D from *H.influenzae* {129}, cytokines {130}, lymphokines {130}, hormones {130}, growth factors {130}, toxin A or B from *C.difficile* {131}, iron-uptake proteins {132}, *etc.* Where a mixture comprises capsular saccharides from both serogroups A and C, it may be preferred that the ratio (w/w) of MenA saccharide:MenC saccharide is greater than 1 (*e.g.* 2:1, 3:1, 4:1, 5:1, 10:1 or higher). Different saccharides can be conjugated to the same or different type of carrier protein. Any suitable conjugation reaction can be used, with any suitable linker where necessary.

Toxic protein antigens may be detoxified where necessary *e.g.* detoxification of pertussis toxin by chemical and/or genetic means {63}.

Where a diphtheria antigen is included in the composition it is preferred also to include tetanus antigen and pertussis antigens. Similarly, where a tetanus antigen is included it is preferred also to include diphtheria and pertussis antigens. Similarly, where a pertussis antigen is included it is preferred also to include diphtheria and tetanus antigens.

Antigens in the composition will typically be present at a concentration of at least 1μg/ml each. In general, the concentration of any given antigen will be sufficient to elicit an immune response against that antigen.

As an alternative to using protein antigens in the composition of the invention, nucleic acid encoding the antigen may be used {*e.g.* refs. 133 to 141}. Protein components of the compositions of the invention may thus be replaced by nucleic acid (preferably DNA *e.g.* in the form of a plasmid) that encodes the protein.

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The invention also provides a process for producing a polypeptide of the invention, comprising the step of culturing a host cell transformed with nucleic acid of the invention under conditions which induce polypeptide expression.

The invention provides a process for producing a polypeptide of the invention, comprising the step of synthesising at least part of the polypeptide by chemical means.

The invention provides a process for producing nucleic acid of the invention, comprising the step of amplifying nucleic acid using a primer-based amplification method (*e.g.* PCR).

The invention provides a process for producing nucleic acid of the invention, comprising the step of synthesising at least part of the nucleic acid by chemical means.

The invention also provides a process for detecting the presence of a bacterium in a sample, comprising the step of contacting the sample with nucleic acid of the invention under hybridizing conditions; and (b) detecting the presence or absence of hybridization of nucleic acid of the invention to nucleic acid present in the sample. The presence of hybridization in step (b) indicates that the sample contains the relevant bacterium.

The invention also provides an immunoassay method for detecting the presence of a bacteirum, comprising the step of contacting a sample with a polypeptide or antibody of the invention.

Adhesion inhibition

The invention provides methods for inhibiting the attachment of bacterial cells to host cells (*e.g.* human cells). The cell may be *in vitro* (*e.g.* in cell culture) or *in vivo*. The cells are most preferably human cells. The host cells will typically be epithelial or endothelial cells.

The invention provides a method for preventing the attachment of a bacterial cell to a host cell, wherein the ability of one or more of the polypeptides of the invention to bind to the host cell is blocked.

The ability to bind may be blocked in various ways but, most conveniently, an antibody specific for a polypeptide of the invention is used. As an alternative to using antibodies, antagonists of the interaction between the polypeptide of the invention and its receptor on the host cell may be used. As a further alternative, a soluble form of the host cell receptor may be used as a decoy. These can be produced by removing the receptor's transmembrane and, optionally, cytoplasmic regions.

The antibodies, antagonists and soluble receptors of the invention may be used as medicaments to prevent the attachment of a bacterial cell to a host cell.

The invention provides a method for preventing the attachment of a bacterial cell to a host cell, wherein expression of a polypeptide of the invention is inhibited. The inhibition may be at the level

transcription and/or translation. A preferred technique for inhibiting expression of the gene is antisense {*e.g.* refs. 142 to 148, *etc.*}. Antibacterial antisense techniques are disclosed in, for example, references 149 & 150.

The invention provides a method for preventing the attachment of a Neisserial cell to an epithelial cell, wherein the gene encoding the polypeptide of the invention is knocked out. Thus the invention provides a bacterium in which such genes have been knocked out. Techniques for producing knockout bacteria are well known. The knockout mutation may be situated in the coding region of the gene or may lie within its transcriptional control regions (*e.g.* within its promoter). The knockout mutation will reduce the level of mRNA encoding a polypeptide of the invention to <1% of that produced by the wild-type bacterium *e.g.* <0.5%, <0.1%, 0%. The knockout mutants of the invention may be used as immunogenic compositions (*e.g.* as vaccines). Such a vaccine may include the mutant as a live attenuated bacterium.

The invention also provides methods for screening compounds to identify those (antagonists) which inhibit the binding of a bacterial cell to a host cell.

Potential antagonists for screening include small organic molecules, peptides, peptoids, polypeptides, lipids, metals, nucleotides, nucleosides, polyamines, antibodies, and derivatives thereof. Small organic molecules have a molecular weight between 50 and about 2,500 daltons, and most preferably in the range 200-800 daltons. Complex mixtures of substances, such as extracts containing natural products, compound libraries or the products of mixed combinatorial syntheses also contain potential antagonists.

Typically, a polypeptide of the invention is incubated with a host cell and a test compound (*e.g.* an antibody), and the mixture is then tested to see if the interaction between the protein and the epithelial cell has been inhibited. The protein, cell and compound may be mixed in any order.

Inhibition will, of course, be determined relative to a standard (*e.g.* the native protein/cell interaction). Preferably, the standard is a control value measured in the absence of the test compound. It will be appreciated that the standard may have been determined before performing the method, or may be determined during or after the method has been performed. It may also be an absolute standard.

For preferred high-throughput screening methods, all the biochemical steps for this assay are performed in a single solution in, for instance, a test tube or microtitre plate, and the test compounds are analysed initially at a single compound concentration. For the purposes of high throughput screening, the experimental conditions are adjusted to achieve a proportion of test compounds identified as "positive" compounds from amongst the total compounds screened.

e method may also simply involve incubating one or more test compound(s) with a polypeptide of the invention and determining if they interact. Compounds that interact with the protein can then be tested for their ability to block an interaction between the protein and an epithelial cell.

Other methods which may be used include, for example, reverse two hybrid screening {151} in which the inhibition of the bacteria:host receptor interaction is reported as a failure to activate transcription.

The invention also provides a compound identified using these methods. These can be used to treat or prevent bacterial infection. The compound preferably has an affinity for App, ORF40 and/or NadA of at least 10^{-7} M *e.g.* 10^{-8} M, 10^{-9} M, 10^{-10} M or tighter.

Definitions

The term "comprising" means "including" as well as "consisting" *e.g.* a composition "comprising" X may consist exclusively of X or may include something additional *e.g.* X + Y.

The term "about" in relation to a numerical value *x* means, for example, $x \pm 10\%$.

References to a percentage sequence identity between two amino acid sequences means that, when aligned, that percentage of amino acids are the same in comparing the two sequences. This alignment and the percent homology or sequence identity can be determined using software programs known in the art, for example those described in section 7.7.18 of reference 152. A preferred alignment is determined by the Smith-Waterman homology search algorithm using an affine gap search with a gap open penalty of 12 and a gap extension penalty of 2, BLOSUM matrix of 62. The Smith-Waterman homology search algorithm is disclosed in reference 153.

BRIEF DESCRIPTION OF THE DRAWINGS

Figures 1 to 15 show analyses of amino acid sequences of the invention to show coiled-coil regions.

Figure 16 shows conservation between anchor regions of polypeptides of the invention.

Figure 17 is an illustration of the NadA structure within the meningococcal outer membrane, in monomeric and trimeric form.

Figures 18 & 19 show comparisons of the genetic environment of genes encoding polypeptides of the invention. Figure 20 illustrates the genetic environment in *E.coli* K1 *vs.* K12.

MODES FOR CARRYING OUT THE INVENTION

Neisseria meningitidis* NadA *protein

Within the *Neisseria meningitidis* serogroup B genome {75}, an outer membrane protein (NadA) was identified {1} which shows weak homology to *Yersinia enterocolitica* adhesin YadA and to *Moraxella catarrhalis* surface protein UspA2 {154}. The *nadA* gene is present in a subgroup of

pervirulent *N.meningitidis* strains and is characterized by a low GC content, which suggests a probable acquisition event of the gene by horizontal transfer.

To investigate the possibility that proteins similar to the NadA adhesin could have been acquired by other pathogens, we searched for homologous proteins.

A sequence alignment of NadA & YadA revealed that the two proteins are most similar at the C-terminus, which is the membrane anchor domain. In NadA, this domain is approximately 70 residues long and contains five predicted amphipatic beta strands, which cross the outer membrane multiple times thus anchoring the protein to the surface of the bacterium (Figure 17). Within this region, the level of sequence similarity between NadA & YadA is around 60% identity while in the N-terminal and central domain the homology is below 25% identity.

In a first search, based on the NadA anchor domain, results included YadA and UspA2, but also other proteins, such as the serum resistance protein DsrA of *Haemophilus ducreyi*, the immunoglobulin binding proteins EibA-C-D-E and F of *E.coli*, and the outer membrane protein 100 of *Actinobacillus actinomycetemcomitans* {154}. In order to highlight more distant members of this family, these results were used for further searches, and this approach identified 16 further results. These 16 polypeptides were further evaluated for secondary structure analysis, coiled coil prediction and presence/absence of a leader peptide. As expected, despite the little amino acid similarity displayed within the central regions, most of the identified polypeptides possess the coiled coil feature, which gives them the capability to form stable oligomers. The anchor regions of the identified polypeptides are well conserved (Figure 16). In addition, the GC content of the genes encoding these polypeptides was lower than average for their respective genomes, suggesting that they are encoded by genes carried on mobile genetic elements.

Escherichia coli

Polypeptides were found in pathogenic strains of *E.coli*, including enteropathogenic (EPEC), enteroaggregative (EAEC), enterohemorragic (EHEC) and uropathogenic (UPEC) strains. Furthermore, a polypeptide almost identical to those of the EHEC and EPEC strains was found in the K1 strain, which is a capsulated *E.coli* strain responsible for neonatal meningitis. The K1 sequence aligns with NadA as follows:

```
        100        110        120        130        140        150
k1.pep    TGVVQIPARYQSMINARQSAVTDAQQTQITEQQAQIVATQKTLAATGDTQNTAHYQEMIN
                                          | :::||  :: | |::|| :  :: | :|
NadA.pep DAALADTDAALDETTNALNKLGENITTFAEETKTNIVKIDEKLEAVADTVD--KHAEAFN
         130        140        150        160        170          180

        160        170        180        190        200        210
k1.pep    ARLAAQNEANQRTTTEQGQKMNALTTDVAAQQQKERAQYDKQMQSLAQKSVQAHEQIESL
              : :|:|  | ::::: |    : ::| : :::      |  :: | |:  |    ::
NadA.pep DIADSLDETN--TKADEAVKTANEAKQTAEETKQNVDAKVKAAETAAGKAEAAAGTANTA
           190          200        210        220        230        240

        220        230        240        250        260        270
```

```
k1.pep    RQDSAQTQQQLTNTQKRVADNSQQINTLNNHFDSLKNEVEDNRKEANAGTASAIAIASQP
           : :   :  ::|: :  :| |: :|   : ::||| ::| : |||:  | |   |:::
NadA.pep ADKAEAVAAKVTDIKADIATNKADIAKNSARIDSLDKNVANLRKETRQGLAEQAALSGLF
              250       260       270       280       290       300

       280       290       300       310       320       330
k1.pep    QVKTGDVMMVSAGAGTFNGESAVSVGTSFNAGTHTVLKAGISADTQSDFGAGVGVGYSF
          |  :    : |:|::| :::||||::||:|    : : |||::: |:|  :|:  || ::
NadA.pep QPYNVGRFNVTAAVGGYKSESAVAIGTGFRFTENFAAKAGVAVGTSSGSSAAYHVGVNYEW
              310       320       330       340       350       360
```

24.4% identity in 209 aa overlap

Another NadA analogue was encoded by the large virulence plasmid present in shiga toxigenic strains of *E.coli* (STEC) {155}. This protein (Saa) is expressed on the outer membrane of *E.coli* and forms high molecular weight oligomers. In contrast, no counterpart of NadA could be detected in the benign *E.coli* strain K12, supporting the view that these genes have been acquired by lateral exchange early during evolution of the species (Figure 20). Nor could a counterpart be seen in laboratory strain MG1655.

Prompted by these observations, and in order to assess a possible mechanism of insertion/deletion of these genes, the arrangement of the region that harbours the gene coding for the NadA-like molecule was investigated. The sequence of this region for the EHEC strain is SEQ ID NO: 23

This analysis showed that the gene organisation of the DNA segments is almost identical among the genomes of K1, EHEC and EPEC, with a sequence conservation of the NadA-like proteins that ranges from 95% identity between K1 and EHEC to 98% identity between K1 and EPEC. In the case of EAEC, although the flanking regions are conserved, the sequence of the NadA-like protein is 380 residues longer than the others, even if the N-terminus and C-terminus are well conserved.

Bacterium	Amino acid	Nucleic acid	Figure
E.coli K1 & *E.coli* EHEC strain EDL933	SEQ ID NO: 2	SEQ ID NO: 22	3
E.coli EPEC strain E2348/69	SEQ ID NO: 7	SEQ ID NO: 24	–
E.coli EAEC strain O42	SEQ ID NO: 8	SEQ ID NO: 25	4

Extending the analysis to the K12 genome, the insertion site was found to be between two hypothetical open reading frames (*YbbJ* and *YbbI*) coded on opposite strands, and that the small "island" consists of three genes: an ORF coding for an hypothetical integral membrane protein, the gene for the putative NadA-like adhesin, and an ORF for a predicted lipoprotein of unknown function. The two latter ORFs are probably co-transcribed, while the first one is coded on the reverse orientation. A couple of 7-bp direct repeats (CTGACGC) that could represent putative insertion sites could be mapped at the boundaries of the inserted fragments (SEQ ID NO: 23, starting at nucleotides 1811 & 4255), and this repeat is absent in the vicinities of the point of insertion in the K12 strain.

The length of the acquired DNA regions is 2348 bases for EPEC, 2450 bases for K1 and EHEC, and 2630 for EAEC (Figure 18). In all cases, the G+C content of the fragment is lower if compared to the

erage composition calculated for each genome, thus confirming the preliminary hypothesis that this segment has been acquired by pathogenic *E.coli* by a mechanism of lateral transfer.

In the case of uropathogenic *E.coli* (UPEC), a different DNA segment was found between the *ybbJ* ad *ybbI* genes. This segment is 1342 bp long and encodes a predicted cytoplasmic protein, which is conserved only in *Salmonella typhymurium* LT2, but absent from all the other analyzed strains of *E.coli*. Differently from the other described insertion fragments, no direct repeats could be mapped at the boundaries of this island, whose GC composition is also very similar to the average value. These data could indicate that the NadA-like encoding gene has been inserted later on in place of the c0608 gene. Nevertheless, subsequent search revealed that a gene coding for an homologue of NadA could be found in a different location of the genome of uropathogenic *E.coli* strain CFT073. This protein is more distantly related to NadA and is seen as a member of a second NadA-like family of proteins. Counterparts of this protein are contained in the other pathogenic strains of *E.coli* at analogous locations and, similarly to the first group of *E.coli* NadA-like molecules, the corresponding genes are also encoded on small islands and are not present in the K12 strain (Figure 19). Furthermore, these genes have strong similarities at the 3' end with a frame-shifted *Shigella flexneri* sequence. The arrangement of NLM flanking regions has been compared in the two species (*E.coli* and *Shigella*) revealing striking similarities. Although the sequence conservation is restricted to the amino and carboxy-terminal portions of the adhesin coding genes, the flanking regions are syntenic and share more than 80% identity at the nucleotide level. Upstream of the NadA-like gene, this island contains an ORF coding for a lipoprotein that is frameshifted either in EPEC, EHEC and in *Shigella*. Furthermore, in the genome of *Shigella*, two additional genes (insA and insB), coding for transposase elements are found in the vicinities of the NLM gene.

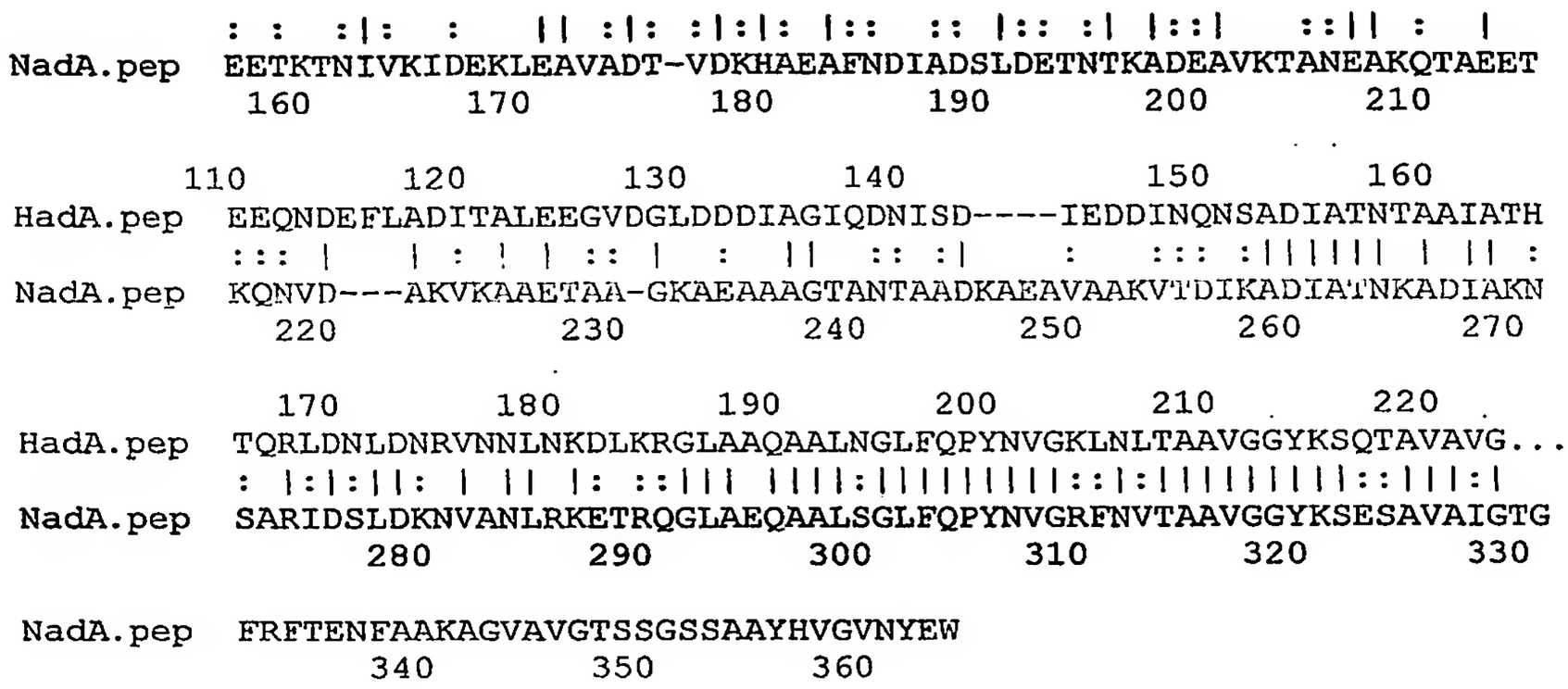
Bacterium	Amino acid	Nucleic acid	Figure
E.coli UPEC strain CFT073	SEQ ID NO: 10	SEQ ID NO: 26	5
E.coli EHEC	SEQ ID NO: 3	SEQ ID NO: 27	6
E.coli EAEC	SEQ ID NO: 9	SEQ ID NO: 28	7
E.coli EPEC	SEQ ID NO: 18	SEQ ID NO: 30	8
S.flexneri	SEQ ID NO: 11	SEQ ID NO: 31	9

Haemophilus

An incomplete NadA homolog was found in Brazilian purpuric fever (BPF) *Haemophilus influenzae* isolates {156}. This polypeptide has been named HadA. NadA and HadA align as follows:

```
                                  10         20         30         40
HadA.pep                MKRNLLKQSVIAVLIGGTTVSNYALAQAQAQAQVKKDELSELKKQVKEM-
                                                :: |||:::|  :   : |::| :::  :
NadA.pep   KTVNENKQNVDAKVKAAESEIEKLTTKLADTDAALADTDAALDETTNALNKLGENITTFA
            100        110        120        130        140        150

          50         60         70         80         90        100
HadA.pep   DAAIDGILDDNIAYEAEVDAKLDQHSAALGRHTNRLNNLKTIAEKAKGDSSEALDKIEAL
```



No HadA counterpart could be detected either in non-typeable *H.influenzae* strain 86028, which is responsible for otitis media in children, or in the non-pathogenic *H.influenzae* strain Rd KW20. The very high level of sequence identity between HadA and NadA in the C-terminal anchor region might indicate a common origin.

In order to analyze the origin of the *hadA* gene, the nucleotide sequence of this DNA region in the BPF isolate (SEQ ID NO: 20) was compared to the same region in the genome sequence for *H.influenzae* strains: the non-pathogenic strain Rd {157}, and a non-typeable 86028 strain (NTHi 86028), associated with pediatric otitis media disease.

The results of this comparison indicate that the adhesin coding gene is specific for the Brazilian Purpuric Fever clone (strain F3031), while no counterparts could be mapped either in the laboratory Rd or in the non-typeable strains. The HadA-encoding fragment has an organization that closely resembles that described for NadA {1} and includes an intact open reading frame plus a 182 bp upstream region, which contains –10 and –35 promoter elements. The small genetic island is flanked by the RNA helicase gene at the 5' end and by a putative protease encoding gene located at the 3' end. The GC composition of the recombined segment is consistent with the rest of the genome.

In contrast, while the NTHi 86028 strain can be regarded as a totally negative strain as it lacks the whole region encompassing the RNA helicase and protease ORFs, the Rd genome contains at this location a DNA segment of 1.1 kb, which encodes two short ORFs of unknown function. This region is characterized by an abnormal GC content (32%) thus suggesting that an independent recombination event has taken place at this site.

Additional NadA-like molecules were identified in other *Haemophilus* species, namely *H.somnus, H.ducreyi and H.actinomycetemcomitans* (also known as *Actinobacillus actinomycetemcomitans*).

Bacterium	Amino acid	Nucleic acid	Figure
H.influenzae biogroup *aegyptius*	SEQ ID NO: 1	SEQ ID NO: 20	1
H.somnus strain 129PT	SEQ ID NO: 5	SEQ ID NO: 21	2

H.ducreyi	SEQ ID NO: 6	–	–
H.actinomycetemcomitans	SEQ ID NO: 4	–	–

NadA and the *H.actinomycetemcomitans* sequence align as follows:

```
                    10         20         30         40          50
actac.pe  MTYQLFKHHLVALMVTGAISVNALAKDSFLENPSANLPQQVFKNR--VD--IFNNETNI
                                          |::   :|| : | :|:   ||   :    |::|
NadA.pep  TIYDIGEDGTITQKDATAADVEADDFKGLGLKKVVTNLTKTVNENKQNVDAKVKAAESEI
           60         70         80         90         100        110

             60         70         80         90         100        110
actac.pe  NENKKDIAINKANIASIEKDVMRNTGGIDRLAKQELVNRARITKNELDIRKNTKSIAENT
          ::     :| : | :|: :   : ::|:::::|:::         ||     : : |   :| |:
NadA.pep  EKLTTKLADTDAALADTDAALDETTNALNKLGEN--------ITTFAEETKTNIVKIDEKL
          120        130        140        150                 160        170

                120        130        140                150        160
actac.pe  ASIA-RIDGNLEGVNRVLQNVDVRSTE--------NAARSRANE--QKIAENKKAIENKA
           ::|   :| : |: | : :::|   :|:         | |:: |:|   |::   : || |: |
NadA.pep  EAVADTVDKHAEAFNDIADSLDETNTKADEAVKTANEAKQTAEETKQNVDAKVKAAETAA
                   180        190        200        210        220        230

             170        180        190        200        210        220
actac.pe  DKADVEKNRADIAAN-SRAIAT-FRSSSQNIAALTTKVDRNTARIDRLDSRVNELDKEVK
           ||::   : |: ||: ::|:|:    : : :||:   : : :|:|||| ||: | :| ||::
NadA.pep  GKAEAAAGTANTAADKAEAVAAKVTDIKADIATNKADIAKNSARIDSLDKNVANLRKETR
                   240        250        260        270        280        290

                230        240        250        260        270        280
actac.pe  NGLASQAALSGLFQPYNVGSLNLSAAVGGYKSKTALAVGSGYRFNQNVAAKAGVAVSTN-
          :||| |||||||||||||| :|::|||||||::|:|:|:|:||::| ||||||||:|:
NadA.pep  QGLAEQAALSGLFQPYNVGRFNVTAAVGGYKSESAVAIGTGFRFTENFAAKAGVAVGTSS
                   300        310        320        330        340        350

                290
actac.pe  GGSATYNVGLNFEW
          |:||:|:||:|:||
NadA.pep  GSSAAYHVGVNYEW
                   360
```

37.0% identity in 284 aa overlap

NadA and the *H.somnus* sequence align as follows:

```
                    90         100        110        120        130        140
H.somnus.pep EVIKGWNEVKSLPRIDGNGKDKQTKDQIAMLIRTVDNTKELGRIVSTNIEDIKNLKKELY
                                          |   | |:   :: : :::  |     |   :|:
    NadA.pep         MSMKHFPSKVLTTAILATFCSGALAATSDD--DVKKAATVAIVAAYNNGQEIN
                              10         20         30         40         50

                     150        160        170        180        190
H.somnus.pep GF-----VEDVNES---EARNISRIDENEKDIKNL--KKELYDFVEDVNESEARNISRID
             ||     : |::|:     :: :  | :  |:|:|  || : :::: |||::    :::
    NadA.pep GFKAGETIYDIGEDGTITQKDATAADVEADDFKGLGLKKVVTNLTKTVNENKQNVDAKVK
                     60         70         80         90         100        110

                  200        210        220        230        240        250
H.somnus.pep ENEKDINTLK-ELMDED--LNSVLTQIEDVKLTFQDVNDNVNLAFEEINGNAQKFDTAIE
               |::|: |  :| | |  | :: : ::::  ::: :::|::   || : |  |:|  :|
    NadA.pep AAESEIEKLTTKLADTDAALADTDAALDETTNALNKLGENITTFAEETKTNIVKIDEKLE
                     120        130        140        150        160        170

                     260        270        280        290        300        310
H.somnus.pep GLTSGLSDLQAKVDANKQETEDDIADNAKAIHSNTKGIAKNTKDIRDLDTKTKQMLENDK
             ::::         || :  |: :||||:    ::::   :|:::: ::   :|||
    NadA.pep AVAD-------TVDKHA-EAFNDIADSLDETNTKADEAVKTANEAKQTAEETKQ------
```

```
                          180       190       200       210

                  320       330       340       350       360       370
H.somnus.pep NLMTGLESLATETSKGFERFDVKTQQLDQAVANVVGRVDITEQAIRQNTAGLVNVNKRVD
             |: : :::  | ::|:     : :   |:| | |:::|   :  |  | | ::: : |:|
  NadA.pep NVDAKVKAAETAAGKAEAAAGTANTAADKAEA-VAAKVTDIKADIATNKADIAKNSARID
             220       230       240       250       260       270

                       380       390       400       410       420
H.somnus.pep TLDKN-------TKAGIASAVALGMLPQSTAPGKSLVSLGVGHHRGQSATAIGVSSMSSN
             :||||       |: |:|  :||: | |    |:  |: :|| ::::||:||| :::  :
  NadA.pep SLDKNVANLRKETRQGLAEQAALSGLFQPYNVGRFNVTAAVGGYKSESAVAIG-TGFRFT
              280       290       300       310       320       330

                 430       440       450
H.somnus.pep GKWVVKGGMSYDTQRHATFGGSVGFFFN
              ::::|:|::  |:  :: :  ||
  NadA.pep ENFAAKAGVAVGTSSGSSAAYHVGVNYEW
             340       350       360
```

23.2% identity in 354 aa overlap

NadA and the *H.ducreyi* sequence align as follows:

```
                150       160       170       180       190       200
H.ducreyi.pe SKNKQNIDTISKYLLELGTYLDGSYRMMEQNTHNINKNTHNINKNTHNINKLSKELQTGL
                                          |  :| ||:  |::  :|: :| || : ||
  NadA.pep EAAAGTANTAADKAEAVAAKVTDIKADIATNKADIAKNSARIDSLDKNVANLRKETRQGL
                240       250       260       270       280       290

                210       220       230       240       250       260
H.ducreyi.pe ANQSALSMLVQPNGVGKTSVSAAVGGYRDKTALAIGVGSRITDRFTAKAGVAFNTYNGG-
             |:|:||| | || :||: :|:||||||:::|:|||:| |:|: |:|||||| :| :|:
  NadA.pep AEQAALSGLFQPYNVGRFNVTAAVGGYKSESAVAIGTGFRFTENFAAKAGVAVGTSSGSS
             300       310       320       330       340       350

                270
H.ducreyi.pe MSYGASVGYEF
              :| ::|:||:
  NadA.pep AAYHVGVNYEW
             360
```

47.5% identity in 101 aa overlap

NB: the coiled-coil prediction for the *H.ducreyi* polypeptide is not high.

Other bacteria

Further NadA homologs identified in the search are:

Bacterium	Amino acid	Nucleic acid	Figure
Brucella melitensis	SEQ ID NO: 12	SEQ ID NO: 32	10
Brucella suis	SEQ ID NO: 13	SEQ ID NO: 33	11
Ralstonia solanacearum	SEQ ID NO: 14	SEQ ID NO: 34	12
Sinorhizobium meliloti	SEQ ID NO: 15	SEQ ID NO: 35	13
Bradorhizobium japonicum	SEQ ID NO: 16	SEQ ID NO: 36	14
Burkholderia fungorum	SEQ ID NO: 17	SEQ ID NO: 29	15

Multiple sequence alignment

A multiple sequence alignment of members of the NadA "family" is below:

```
        10        20        30        40        50        60
```

```
                   |             |             |             |             |             |
961_HI        ------MKRNLLKQSVIAVLIGGTTVSN--------------------------------
961_ACTAC     ------MTYQLFKHHLVALMVTGAISVNAL------------------------------
MenB NadA     -MSMKHFPSKVLTTAILATFCSGALAATSDDDVKK---AATVAIVAAYNNGQEINGFKAG
YADA_YEREN    --MTKDFKISVSAALISALFSSPYAFADDYDGIPN---LTAVQISPNADPALGLEYPVRP
961_HAESO     MKKVQFFKYSSLALALGLGVSASALAAPTSTSTTTGPEAPPTGPAPTAKDPLAETALAYD
961_K1        ---MKTVNVALLALIISATSSPVVLAGDTIEAAAT-------------------------
961_HAEDU     ------MKIKCLVAVVGLACSTITTMAQQP------------------------------
                    .          :
Prim.cons.    M23MK42K22LLA2AI2A2FS2GALAA2T6D444TGPEA33V3I3P3A333L33333333

                  70        80        90       100       110       120
                   |         |         |         |         |         |
961_HI        --------------YALAQAQAQAQVKKD-------------------------------
961_ACTAC     ---------AKDSFLENPSANLPQQVFKNR---VDIFNNET-------------------
MenB NadA     ETIYDIGEDGTITQKDATAADVEADDFKGLGLKKVVTNLTK-------------------
YADA_YEREN    PVPGAGGLNASAKGIHSIAIGATAEAAKGAAVAVGAGSIATGVNSV-----------AIG
961_HAESO     LENEVAYLRMKAGEWMQLGLDPEKEVIKGWNEVKSLPRIDGNGKDKQTKDQIAMLIRTVD
961_K1        --------ELSAINSGMSQSEIEQKITRFLERTDNSPAAYT-------------------
961_HAEDU     ----------PKFAGVSSLYSYEYDYGKGK------------------------------
                                      .   :
Prim.cons.    333333GL4A2A6677SS2ADAEA3VFKGL444255PNI5T22222QTKDQIAMLIR222

                 130       140       150       160       170       180
                   |         |         |         |         |         |
961_HI        ELSELKKQVKEMDAAIDGILDDNIAYEAEVDAKLDQHSAALGRHTNRLNNLKT-------
961_ACTAC     NINENKKDIAINKANIASIEKDVMRNTGGIDRLAKQELVNRARITKNELDIR--------
MenB NadA     TVNENKQNVDAKVKAAESEIEKLTTKLADTDAALADTDAALDETTNALNKLGE-------
YADA_YEREN    PLSKALGDSAVTYGAASTAQKDGVAIGARASTSDTGVAVGFNSKADAKNSVAIGHSSHVA
961_HAESO     NTKELGRIVSTNIEDIKNLKKELYGFVEDVNESEARNISRIDENEKDIKNLKK-------
961_K1        YLTEHHYIPSETPDTTQTPPVQTDPDAGQKTVAATGVVQIPARYQSMINARQS-------
961_HAEDU     WTWSNEGGFDIKVPGIKMKPKEWISKQATYLELQHYMPYTPVLVTSAPDVSPS-------
                 .                 .                    .
Prim.cons.    NL2ENK22V323VAAIK2IPKDLIAK7ADVD23222V72A22R7T3A2NNLKSGHSSHVA

                 190       200       210       220       230       240
                   |         |         |         |         |         |
961_HI        ----------------------------------IAEKAKGDSSEALDKIEALEEQNDE-
961_ACTAC     ----------------------------------KNTKSIAENTASIARIDGNLEGVNR-
MenB NadA     ----------------------------------NITTFAEETKTNIVKIDEKLEAVADT
YADA_YEREN    ANHGYSIAIGDRSKTDRENSVSIGHESLNRQLTHLAAGTKDTDAVNVAQLKKEIEKTQEN
961_HAESO     ------------------------------ELYDFVEDVNESEARNISRIDENEKDINTL
961_K1        ---------------------------------AVTDAQQTQITEQQAQIVATQKTLAAT
961_HAEDU     -----------------------------------SISILLYPMSDPDQLGINRQQLKLN
                                                            ::     :
Prim.cons.    ANHGYSIAIGDRSKTDRENSVSIGHESLNR2L236A2K7KEE72ENIAQID2N2EQ22E2

                 250       260       270       280       290       300
                   |         |         |         |         |         |
961_HI        -------------FLADITALEEG----------------------VDGLDDDIAGIQDN
961_ACTAC     -------------VLQNVDVRSTENAA------------------RSRANEQKIAENKKA
MenB NadA     VDKHAEAFNDIADSLDETNTKADEAVK------------------TANEAKQTAEETKQN
YADA_YEREN    TNKRS------AELLANANAYADNKSSSV-LGIANNYTDSKSAETLENARKEAFAQSKDV
961_HAESO     KELMDEDLNSVLTQIEDVKLTFQDVNDNVNLAFEEINGNAQKFDTAIEGLTSGLSDLQAK
961_K1        GDTQN---TAHYQEMINARLAAQNEAN----------------QRTTTEQGQKMNALTTD
961_HAEDU     -----------LYSYFNDLPHDFK----------------------LKVLDARISKNKQN
                          : :
Prim.cons.    4DK44E22N34257LA22227A225A52VNL222222222223TT7N3L2QKIAE2K2N

                 310       320       330       340       350       360
                   |         |         |         |         |         |
961_HI        ISDIED-----------------------------------DINQNSADIATNTAAIATH
961_ACTAC     IENKADKA---------------------------------DVEKNRADIAANSRAIATF
MenB NadA     VDAKVKAA---------------------------------ETAAGKAEAAAGTANTAAD
YADA_YEREN    LNMAKAHSNSVARTTLETAEEHANSVAR-----TTLETAEEHANKKSAEALASANVYADS
961_HAESO     VDANKQETEDDIADNAKAIHSNTKGIAKNTKDIRDLDTKTKQMLENDKNLMTGLESLATE
961_K1        VAAQQQKE--------------------------------RAQYDKQMQSLAQKSVQAHE
961_HAEDU     IDTISK-----------------------------------YLLELGTYLDGSYRMMEQN
              :
Prim.cons.    2DA2K3KA2222222222222222222A2NTKDI22L2T223D722NSA23AA3T22IATE

                 370       380       390       400       410       420
                   |         |         |         |         |         |
961_HI        ------------------------------------TQRLDNLDNRVNNLNKDLKRGLAA
961_ACTAC     RSS---SQ---------NIAALTTKVDR-------NTARIDRLDSRVNELDKEVKNGLAS
MenB NadA     KAE---AVAAKVTDIKADIATNKADIAK-------NSARIDSLDKNVANLRKETRQGLAE
YADA_YEREN    KSS---HTLKTANSYTDVTVSNSTKKAIRESNQ-YTDHKFRQLDNRLDKLDTRVDKGLAS
```

```
961_HAESO     TSKGFERFDVKTQQLDQAVANVVGRVDITEQAIRQNTAGLVNVNKRVDTLDKNTKAGIAS
961_K1        QIES---LRQDSAQTQQQLTNTQKRVADNSQQINTLNNHFDSLKNEVEDNRKEANAGTAS
961_HAEDU     THN------------------IN-----------KNTHNINKNTHNINKLSKELQTGLAN
                                                :     .:    .    * *
Prim.cons.    2S22FE4544K44Q44Q5IANN6T2VAI3EQ3I24NTARID2LDNRVN2LDKE3KAGLAS

                        430       440       450       460       470       480
                         |         |         |         |         |         |
961_HI        QAALNGLFQPYNVGKLNLTAAVGGYKSQTAVAVG-------------------------
961_ACTAC     QAALSGLFQPYNVGSLNLSAAVGGYKSKTALAVGSG-YRFNQNVAAKAGVAVST-N-GGS
MenB_NadA     QAALSGLFQPYNVGRFNVTAAVGGYKSESAVAIGTG-FRFTENFAAKAGVAVGTSS-GSS
YADA_YEREN    SAALNSLFQPYGVGKVNFTAGVGGYRSSQALAIGSG-YRVNENVALKAGVAYAG---SSD
961_HAESO     AVALGMLPQSTAPGKSLVSLGVGHHRGQSATAIGVSSMSSNGKWVVKGGMSYDTQR-HAT
961_K1        AIAIASQPQVKTGDVMMVSAGAGTFNGESAVSVGTS-FNAGTHTVLKAGISADTQS-DFG
961_HAEDU     QSALSMLVQPNGVGKTSVSAAVGGYRDKTALAIGVG-SRITDRFTAKAGVAFNTYNGGMS
                *:    *    .   .: ..* .... * ::*          :::*:*::: :
Prim.cons.    QAALSGLFQPYNVGKLNVSAAVGGY2S32A2AIG3GS2RFNEN2AAKAGVA2DTQ2GGSS

                        490
                         |
961_HI        ----------
961_ACTAC     ATYNVGLNFEW
MenB_NadA     AAYHVGVNYEW
YADA_YEREN    VMYNASFNIEW
961_HAESO     --FGGSVGFFFN
961_K1        --AGVGVGYSF
961_HAEDU     --YGASVGYEF
                 :  :: : :
Prim.cons.    AGY2VGVNFEW
```

It will be understood that the invention has been described by way of example only and modifications may be made whilst remaining within the scope and spirit of the invention.

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SEQUENCE LISTING

SEQ ID NO: 1 **(Haemophilus aegyptius)**

MKRNLLKQSVIAVLIGGTTVSNYALAQAQAQAQVKKDELSELKKQVKEMDAAIDGILDDNIAYEAEVDAKLDQHSAALGRHTNRLNNL
KTIAEKAKGDSSEALDKIEALEEQNDEFLADITALEEGVDGLDDDIAGIQDNISDIEDDINQNSADIATNTAAIATHTQRLDNLDNRV
NNLNKDLKRGLAAQAALNGLFQPYNVGKLNLTAAVGGYKSQTAVAVG

SEQ ID NO: 2 **(Escherichia coli)**

MKTVNVALLALIISATSSPVVLAGDTIEAAATELSAINSGMSQSEIEQKITRFLERTDNSPAAYTYLTEHHYIPSETPDTTQTPTVQT
DPDAGQKTVAATGDVQTTARYQSMINARQSAVTDAQQTQITEQQAQIVATQKTLAATGDTQNTAHYQEMINARLAAQNEANQRTATEQ
GQKMNALTTDVAVQQQNERTQYDKQMQSLAQESAQAHEQIDSLSQDVTQTHQQLTNTQKRVADNSQQINTLNNHFSSLKNEVDDNRKE
ANAGTASAIAIASQPQVKTGDVMMVSAGAGTFNGESAVSVGTSFNAGTHTVLKAGISADTQSDFGAGVGVGYSF

SEQ ID NO: 3 (EHEC)

MNKIFKVIWNPATGNYTVTSETAKSRGKKSGRSKLLISALVAGGMLSSFGALANAGNDNGQGVDYGSGSAGDGWVAIGKGAKANTFMNTSGSSTAVG
YDAIAEGQYSSAIGSKTHAIGGASMAFGVSAISEGDRSIALGASSYSLGQYSMALGRYSKALGKLSIAMGDSSKAEGANAIALGNATKATEIMSIAL
GDTANASKAYSMALGASSVASEENAIAIGAETEAAENATAIGNNAKAKGTNSMAMGFGSLADKVNTIALGNGSQALADNAIAIGQGNKADGVDAIAL
GNGSQSRGLNTIALGTASNATGDKSLALGSNSSANGINSVALGADSIADLDNTVSVGNSSLKRKIVNVKNGAIKSDSYDAINGSQLYAISDSVAKRL
GGGAAVDVDDGTVTAPTYNLKNGSKNNVGAALAVLDENTLQWDQTKGKYSAAHGTSSPTASVITDVADGTISASSKDAVNGSQLKATNDDVEANTAN
IATNTSNIATNTANIATNTTNITNLTDSVGDLQADALLWNETKKAFSAAHGQDTTSKITNVKDADLTADSTDAVNGSQLKTTNDAVATNTTNIANNT
SNIATNTTNISNLTETVTNLGEDALKWDKDNGVFTAAHGTETTSKITNVKDGDLTTGSTDAVNGSQLKTTNDAVATNTTNIATNTTNISNLTETVTN
LGEDALKWDKDNGVFTAAHGNNTASKITNILDGTVTATSSDAINGSQLYDLSSNIATYFGGNASVNTDGVFTGPTYKIGETNYYNVGDALAAINSSF
STSLGDALLWDATAGKFSAKHGTNGDASVITDVADGEISDSSSDAVNGSQLHGVSSYVVDALGGGAEVNADGTITAPTYTIANADYDNVGDALNAID
TTLDDALLWDADAGENGAFSAAHGKDKTASVITNVANGAISAASSDAINGSQLYTTNKYIADALGGDAEVNADGTITAPTYTIANAEYNNVGDALDA
LDDNALLWDETANGGAGAYNASHDGKASIITNVANGSISEDSTDAVNGSQLNATNMMIEQNTQIINQLAGNTDATYIQENGAGINYVRTNDDGLAFN
DASAQGVGATAIGYNSVAKGDSSVAIGQGSYSDVDTGIALGSSSVSSRVIAKGSRDTSITENGVVIGYDTTDGELLGALSIGDDGKYRQIINVADGS
EAHDAVTVRQLQNAIGAVATTPTKYFHANSTEEDSLAVGTDSLAMGAKTIVNGDKGIGIGYGAYVDANALNGIAIGSNAQVIHVNSIAIGNGSTTTR
GAQTNYTAYNMDAPQNSVGEFSVGSADGQRQITNVAAGSADTDAVNVGQLKVTDAQVSQNTQSITNLDNRVTNLDSRVTNIENGIGDIVTTGSTKYF
KTNTDGVDASAQGKDSVAIGSGSIAAADNSVALGTGSVATEENTISVGSSTNQRRITNVAAGKNATDAVNVAQLKSSEAGGVRYDTKADGSIDYSNI
TLGGGNGGTTRISNVSAGVNNNDVVNYAQLKQSVQETKQYTDQRMVEMDNKLSKTESKLSGGIASAMAMTGLPQAYTPGASMASIGGGTYNGESAVA
LGVSMVSANGRWVYKLQGSTNSQGEYSAALGAGIQW

SEQ ID NO: 4 **(Actinobacillus actinomycetemcomitans)**

MTYQLFKHHLVALMVTGAISVNALAKDSFLENPSANLPQQVFKNRVDIFNNETNINENKKDIAINKANIASIEKDVMRNTGGIDRLAK
QELVNRARITKNELDIRKNTKSIAENTASIARIDGNLEGVNRVLQNVDVRSTENAARSRANEQKIAENKKAIENKADKADVEKNRADI
AANSRAIATFRSSSQNIAALTTKVDRNTARIDRLDSRVNELDKEVKNGLASQAALSGLFQPYNVGSLNLSAAVGGYKSKTALAVGSGY
RFNQNVAAKAGVAVSTNGGSATYNVGLNFEW

SEQ ID NO: 5 **(Haemophilus somnus)**

MKKVQFFKYSSLALALGLGVSASALAAPTSTSTTTGPEAPPTGPAPTAKDPLAETALAYDLENEVAYLRMKAGEWMQLGLDPEKEVIK
GWNEVKSLPRIDGNGKDKQTKDQIAMLIRTVDNTKELGRIVSTNIEDIKNLKKELYGFVEDVNESEARNISRIDENEKDIKNLKKELY
DFVEDVNESEARNISRIDENEKDINTLKELMDEDLNSVLTQIEDVKLTFQDVNDNVNLAFEEINGNAQKFDTAIEGLTSGLSDLQAKV
DANKQETEDDIADNAKAIHSNTKGIAKNTKDIRDLDTKTKQMLENDKNLMTGLESLATETSKGFERFDVKTQQLDQAVANVVGRVDIT
EQAIRQNTAGLVNVNKRVDTLDKNTKAGIASAVALGMLPQSTAPGKSLVSLGVGHHRGQSATAIGVSSMSSNGKWVVKGGMSYDTQRH
ATFGGSVGFFFN

SEQ ID NO: 6 **(Haemophilus ducreyi)**

MKIKCLVAVVGLACSTITTMAQQPPKFAGVSSLYSYEYDYGKGKWTWSNEGGFDIKVPGIKMKPKEWISKQATYLELQHYMPYTPVLV
TSAPDVSPSSISILLYPMSDPDQLGINRQQLKLNLYSYFNDLRHDFKLKVLDARISKNKQNIDTISKYLLELGTYLDGSYRMMEQNTH
NINKNTHNINKNTHNINKLSKELQTGLANQSALSMLVQPNGVGKTSVSAAVGGYRDKTALAIGVGSRITDRFTAKAGVAFNTYNGGMS
YGASVGYEF

SEQ ID NO: 7 **(EPEC)**

MKTVNVALLALIISATSSPFVLAGDTIEAAATELSAINSGMSQSEIEQKITRFLERTDNSPAAYTYLTEHHYIPSETPDTTQTPPVQT
DPDAGQKTVAATGDVQTTARYQSMINARQSTVTDAQQTQITEQQAQIVATQKTLAATGDTQNTAHYQEMINARLAAQNEANQRTTTEQ
GQKMNALTTDVAAQQQKERAQYDKQMQSLAQKSVQAHEQIESLRQDSAQTQQQLTNTQKRVADNSQQINTLNNHFSSLKNEVEDNRKE
ANAGTASAIAIASQPQVKTGDLMMVSAGAGTFNGESAVSVGTSFNAGTHTVLKAGISADTQSDFGAGVGVGYSF

SEQ ID NO: 8 (EAEC)

MKTVKLSLLAVVVATAVSPSAFAGDTVEAATTELTVIQPGMSQSEIDQKIGRFLERTGNSVAAQNYLIAHDYQTTTPQENTAASPVQP
TNTLNPITNQAQTDRDNGQDTAIQDAQHAANWASLKADDAQHAITVAQTDIDANTAAITDTRNDVSAVQSDVTNIKGDVAHAQSTADH
ANANANTALINGVKLSGAVTENKNNIEQNRSDIADQQKLLASNEQKQIVRDNGQDTAIQDAQHAANWASLKADDAQHAITVAQTDIDA
NKAAITDIRNDVSAVQSDVTNIKGDVAHAQSTADHANANANTALMNGVKLSSAVTENKNNIEQNRSDIADQQKLLASNEQKQIVRDNG
QDTAIQDAQHAANWASMKADDAQHAITVAQTDIDANKAAIADTRNDVSAVQSDVTNIKGDVAHAQSTADHANANANTALINGVKLSGA
VTENKNNIEQNRSDIADQQQQLDETRKIVAATGDVQTAARYQSMIDARQTAAANAQQAQADTQQQQMDDQQKQIDATQKTVSALGDAQ
TNAHYQEMVNAGLRAQNDANARTAAEQKQKIDTLATNQATQQHINSVQYGEQIQRLAQDSTQTHEQIDSLTQDVTQTHQQLSNTQKRV
ADNSQQITTLNNHFSSLKNEVEDNRKEANAGTASAIAIASQPQVKAGDFMMMSAGAGTFNGESAVSVGTSFNAGTHTVIKAGVSADTQ
SDFGAGVGVGYSF

SEQ ID NO: 9 (EAEC)

MNKIFKVIWNPATGSYTVASETAKSRGKKSGRSKLLISALVAGGMLSSFGVQAQAGRDNGQGVNYGQGTGTGWVAIGEDAKANSFTDT
GGGSSTAVGYHSTADGRWSTALGAKTHSLGEASVALGINTTSAGERSLAIGASATSTGGFSIALGRYANSVGEFSIAQGDHAETGADD
AIAFGRESKALGIMSIALGATANASKEYAMALGASSAASAANAIAVGRNSAAAGVDSLAFGRQSAASAANAIAMGAESKAAENATAVG
TNAEANGLNSIALGSGSIADVDNTIALGNQSQAVAAGAIAIGQGNKADGANAIALGNGSITGGVNAIALGQGSYAGLENGTAIGAQAS
AQGKNSVALGAGSVATDADTVSVGNTTAQRQIVNMAAGDISTTSTDAINGSQLYAISKSVADNLGGGATVNAQGVVTSPNYRLKSGIF
GTVGDALTGLDNNTLQWDSLKKAYSAAHGTDTTSTITNVKDGAISDTSKDAVNGSQLKTTNDNVATNTANITTNTNSINTLTDSVGDL
KDDALLWNGTAFSAAHGTEATSKITNVKDGDLTAGSTDAVNGSQLKTTNDNVATNTTNITNLTDSVGDLKDDALLWNGTAFSAAHGTD
ATSKITNVKDGDLTAGSTDAVNGSQLKTTNDAVAANTTNIATNTTNITNLTDAVDSLGDDSLLWNATAGAFSAAHGTDATSKITNVTA
GDLTAGSTDAVNGSQLKTTNDAVAANTTNIATNTTNITNLTDAVDSLGDDSLLWNATAGAFSAAHGTDATSKITNVKDGDLTAGSTDA
VNGSQLKTTNDAVAANTTNIATNTTNITNLTDAVDSLGDDSLLWNATAGAFSAKHGTNGTDSKITNLLAGTVSSDSTDAINGSQLYGL
ADSFTSYLGGGADISDAGVLTGPTYTIGGTDYNNVGDALAAINTSFSTSLGDALLWDATAKGGDGAFSAGRGTDNTASIITNVADGAI
SSTSSDAINGSQLYDTSKYIADTLGGDAEVNADGTITAPTYAIAGGSYSNVGDALEAIDTTLDDALLWDATANDGNGAFSAAHGKDKT
ASVITNVANGAISATSSDAINGSQLYTTNKYIADALGGDAEVNADGSITAPTYTIANAEYNNVGDALDALDDNALLWDATANDGAGAY
NASHDGKASIITNVADGNIGEGSTDAINGSQLFNTNMLIQQNSEIINQLAGNTSETYIEDNGAGINYVRTNDNGLAFNDASASGIGAT
AVGYNAVASGESSVAIGQGSSSNVDTGIALGSSSVSSRVIVKGSRDTSVSEEGVVIGYDTTDGELLGALSIGDDGKYRQIINVADGSE
AHDAVTVRQLQNAIGAVATTPTKYFHANSTEEDSLAVGEDSLAMGAKTIVNGNAGIGIGYGAYVDANALNGIAIGSNARANHANSIAM
GNGSQTTRGAQTGYAAYNMDAPQNSVGEFSVGSEDGQRQITNVAAGSADTDAVNVGQLKVTDAQVSQNTQSITNLNNQVTNLDTRVTN
IENGIGDIVTTGSTKYFKTNTDGVDANAQGKDSVAIGSGSIAAADNSVALGTGSVANEENTISVGSSTNQRRITNVAAGVNATDAVNV
SQLKSSEAGGVRYDTKADGSVDYSNITLGGGNGGTTRISNVSAGVNNNDAVNYAQLKQSVQETKQYTDQRMVEMDNKLSKTESKLSGG
IASAMAMTGLPQAYTPGASMASIGGGTYNGESAVALGVSMVSANGRWVYKLQGSTNSQGEYSAALGAGIQW

SEQ ID NO: 10 (UPEC)

MNKIFKVIWNPATGSYTVASETAKSRGKKSGRSKLLISALVAGGLLSSFGASADNYTGQPTDYGDGSAGDGWVAIGKGAKANTFMNTS
GASTALGYDAIAEGEYSSAIGSKTLATGGASMAFGVSAKAMGDRSVALGASSVANGDRSMAFGRYAKTNGFTSLAIGDSSLADGEKTI
ALGNTAKAYEIMSIALGDNANASKEYAMALGASSKAGGADSLAFGRKSTANSTGSLAIGADSSSSNDNAIAIGNKTQALGVNSMALGN
ASQASGESSIALGNTSEASEQNAIALGQGSIASKVNSIALGSNSLSSGENAIALGEGSAAGGSNSLAFGSQSRANGNDSVAIGVGAAA
ATDNSVAIGAGSTTDASNTVSVGNSATKRKIVNMAAGAISNTSTDAINGSQLYTISDSVAKRLGGGATVGSDGTVTAVSYALRSGTYN
NVGDALSGIDNNTLQWNKTAGAFSANHGANATNKITNVAKGTVSATSTDVVNGSQLYDLQQDALLWNGTAFSAAHGTEATSKITNVTA
GNLTAGSTDAVNGSQLKTTNDNVTTNTTNIATNTTNITNLTDAVNGLGDDSLLWNKAAGAFSAAHGTEATSKITNVTAGNLTAGSTDA
VNGSQLKTTNDNVTTNTTNIATNTTNITNLTDAVNGLGDDSLLWNKTAGAFSAAHGTDATSKITNVTAGNLTAGSTDAVNGSQLKTTN
DNVTTNTTNIATNTTNITNLTDAVNGLGDDSLLWNKTAGAFSAAHGTDATSKITNVKAGDLTAGSTDAVNGSQLKTTNDNVSTNTTNI
TNLTDAVNGLGDDSLLWNKTAGAFSAAHGTDATSKITNVKAGDLTAGSTDAVNGSQLKTTNDNVSTNTTNITNLTDSVGDLKDDSLLW
NKAAGAFSAAHGTEATSKITNLLAGKISSNSTDAINGSQLYGVADSFTSYLGGGADISDTGVLSGPTYTIGGTDYTNVGDALAAINTS
FSTSLGDALLWDATAGKFSAKHGINNAPSVITDVANGAVSSTSSDAINGSQLYGVSDYIADALGGNAVVNTDGSITTPTYAIAGGSYN
NVGDALEAIDTTLDDALLWDTTANGGNGAFSAAHGKDKTASVITNVANGAVSATSNDAINGSQLYSTNKYIADALGGDAEVNADGTIT
APTYTIANTDYNNVGEALDALDNNALLWDEDAGAYNASHDGNASKITNVAAGDLSTTSTDAVNGSQLNATNILVTQNSQMINQLAGNT
SETYIEENGAGINYVRTNDSGLAFNDASASGIGATAVGYNAVASHASSVAIGQDSISEVDTGIALGSSSVSSRVIVKGTRNTSVSEEG
VVIGYDTTDGELLGALSIGDDGKYRQIINVADGSEAHDAVTVRQLQNAIGAVATTPTKYYHANSTAEDSLAVGEDSLAMGAKTIVNGN
AGIGIGLNTLVLADAINGIAIGSNARANHADSIAMGNGSQTTRGAQTNYTAYNMDAPQNSVGEFSVGSEDGQRQITNVAAGSADTDAV
NVGQLKVTDAQVSQNTQSITNLNTQVTNLDTRVTNIENGIGDIVTTGSTKYFKTNTDGADANAQGKDSVAIGSGSIAAADNSVALGTG
SVADEENTISVGSSTNQRRITNVAAGVNATDAVNVSQLKSSEAGGVRYDTKADGSIDYSNITLGGGNSGTTRISNVSAGVNNNDAVNY
AQLKQSVQETKQYTDQRMVEMDNKLSKTESKLSGGIASAMAMTGLPQAYTPGASMASIGGGTYNGESAVALGVSMVSANGRWVYKLQG
STNSQGEYSAALGAGIQW

SEQ ID NO: 11 **(Shigella flexneri)**

MTNLGEDALKWDKDNGVFTAAHGTETTSKITNVKDGDLTTGSTDAVNGSQLKTTNDAVATNTTNIATNTTNISNLTETVTNLGEDALK
WDKDNGVFTAAHGNNTASKITNILDGTVTATSSDAINGSQLYDLSSNIATYFGGNASVNTDGVFTGPTYKIGETNYYNVGDALAAINS
SFSTSLGDALLWDATAGKFSAKHGTNGDASVITDVADGEISDSSSDAVNGSQLHGVSSYVVDALGGGAEVNADGTITAPTYTIANADY
DNVGDALNAIDTTPDDALLWDADAGENGAFSAAHGKDKTASVITNVANGAISAASSDAINGSQLYTTNKYIADALGGDAEVNADGTIT
APTYTIANAEYNNVGDALDALDDNALLWDKTANGGAGAYNASHDGKASIITNVANGSISEDSTDAVNGSQLNATNMMIEQNTQIINQL
AGNTDATYIEENGAGTNYVRTNDNDLAFNDASASGVGATAVGYNAVASGASSVAIGQNSSSTVDTGIALGSSSVSSRVIAKGSRDTSV
TENGVVIGYDTTDGELLGALSIGDDGKYRQIINVADGSEAHDAVTVRQLQNAIGAVATTPTKYFHANSTAEDSLAVGEDSLAMGAKTV
VNGNAGIGIGLNTLVLADAINGIAIGSNARANHANSIAMGNGSQTTRGAQTGYTAYNMDAPQNSVGEFSVGSEDGQRQITNVAAGSAD
TDAVNVGQLKVTDERVAQNTQSITNLNNQVTNLDTRVTNIENGIGDIVTTGSTKYFKTNTDGVDANAQGKDSVAIGSGSIAAADNSVA
LGTGSVAEEENTISVGSSTNQRRITNVAASVNATDAVNVSQLKSSEAGGVRYDTKADGSIDYSNITLGGGNGSTTRISNVSAGVNNND
AVNYAQLKQSAQETKQYTDQRMVEMDNKLSKTESKLSGGIASAMAMTGLPQAYTPGASMASIGGGTYNGESAVALGVSMVSANGRWVY
KLQGSTNSQGEYSAALGAGIQW

SEQ ID NO: 12 **(Brucella melitensis)**

MSFFKKNISITAMGGLMLSLAVDAAKAEENVSQVKLPPVFVFELVENQGLANIALIRPRVIAPDNNLRPGGIVSGIAGLLTLGQENRN
LISENRQVINNNTTAIGQNRTSISTNAKGVADNRAAIRQNSAAISALGQRVDGLQGQINSARKEARAGAANAAALSGLRYDNRPGKVS
IATGVGGFKGSTALAAGIGYTSKNENARYNVSVAYNEAGTSWNAGASFTLN

SEQ ID NO: 13 **(Brucella suis)**

MSFFKKNISITAMGGLMLSLAVDAAKAEENVSQVKLPPVFVFELVENQGLANIALIRPRVIAPDNNLRPGGIVSGIAGLLTLGQENRN
LISENRQVINNNTTAIGQNSDRIDANAKGVADNRAAIGQNSGRIDANAKGVADNKAAIGRNSGRIDANAKGVADNKTAIGRNSGRIDT
NAKGVADNRAAISQNRGRINANAAGVASNRAAIRQNSAAISALGQRVDGLQGQINSARKEARAGAANAAALSGLRYDNRPGKVSIATG
VGGFKGSTALAAGIGYTSKNENARYNVSVAYNEAGTSWNAGASFTLN

SEQ ID NO: 14 **(Ralstonia solanacearum)**

MVFSAMPQYACAEMLLQNDPGTNCGSVGDAYAWARGDGYSGCKVGYEAAKNLAKGTAFGNSLGQLSPGTNILVYGSTLRAGMNDEVTP
LDSMNIGGHLDVWGASGFHGGVDMNNSAIKNLADGTLSATSTEAVTGRQLNATNTNITNLQNSIKSISSSASLVQQSAAGKDITVAKD
LDGDAVDFSGKKLSDSTTFSRKLTGVAEGTLSATSTDAVSGKQLYTTNQNLSTTNQNLADTNKSLAETNKNVSATTTNITNLQNTIKN
ISGGSAGLVQQSAAGKDITVAKDLDGEAVDFSGKKLSDSTTFSRKLTGVAEGTLSATSTDAVSGKQLYTTNQNLASTNKDLANTNTRL
TTAEGNLSSNTTSITNLQNTIKNISGGSAGLVQQSAAGKDITVAKDLDGDAVDFSGKKLSDSTTFSRKLTGVAEGTLSATSTDAVSGR
QLYTTNQNLSTTNQNLADTNKSLAETNKNVSATTTNITNLQNTVNNISSGSAGLVQQSAAGKDITVAKDLDGDAVDFSGKKLSDSTTF
SRKLTGVAEGTLSATSTDAVSGKQLYTTNQNLSTTNQNLADTNKSLAETNKNVSATTTNITNLQNTVNNISSGSAGLVQQSAAGKDIT
VAKNLDGDAVDFSGKKLSDSTTFSRKLTGVAEGTLSATSTDAVSGKQLYTTNQNLASTNKDLANTNTRLTTAEGNLSSNTTSITNLQN
TIKNISGGSAGLVQQSAAGKDITVAKDLDGDAVDFSGKNLSDSTTFSRKLTGVAEGTLSATSTDAVSGKQLYTTNQNLSTTNQNLADT
NKSLAKTNNNVSATTTNITNLQNTVNNISSGSAGLVQQSAAGKDITVAKDLDGDAVDFSGKKLSDSTTFSRKLTGVAEGTLSATSTDA
VSGKQLYATNQNVSKLSANVTDVSDSVTNIKNTMNTIVNGGGLKYFHANSTLDDAQAMGLESIAFGGAAVAAGMNSMAMGGNARAVAG
NAVALGAGSVADRANTVSVGSAGKERQITNVAAGTADTDAVNVAQLKAAGIINGSGRTNATVTYGTNADGSADYGNVTLGGGNAPAGT
AIHNVAAGTAETDAVNVRQMNAAIASVQKVSNTNDPMFAADGDRAVKRASAKGTHATAMGAAASAGGDQSVATGHNAQSGGDSSVAMG
ANAKATANHAVAVGSGSVANRANTMSVGSAGSERQITNVAAGVQGTDAVNVSQLSQAVYAAVGDLPAGTTARQYTDEQIGMVRQGISQ
VARGAYSGIAAATALTMIPDVDQGKSIAIGIGSATYKGYQAVALGASARISHNLKAKMGVGYSSEGTTVGMGASYQW

SEQ ID NO: 15 **(Sinorhizobium meliloti)**

MALGRQSVSAGSGSLAFGNGSYANSNGSVAIGQSAYAANVRAIAIGGDDAFAWREAEQTKAGGSQSIAMGVRARTKSLVVDDPDTVAN
EADPGGASDAIAIGTDAQANGDRSLAIGRQNQAGNEQSIGIGAGNTATGKLSIGIGSSNVASGEQSLSLGAGNNALGQGSISIGTETT
AGGLRSIAFGVRASTKEANLDIPDDVAAIDAIAIGTNTKANGDRSVSIGTGSQASSGAVSIGDAAKAVGDKSVSIGTESWADGDESVS
IGLVNNAGFEGNDRIKGGQTSVSLGAFNQSPGIEAIAIGARNEANADRSIAIGSRAKTKAADPAQADGGARDAVAIGTDALANDDRSI
SIGWNSSTSLNDSISIGTRATSGSAGDIMIGTGSGTGSTSGQNNVALGVAASQKVKGSSNIAIGDSAGGSREGDNNVAIGTNAGIQFS
ESEHETAVRADLVVSDAVSIGNEALASADEAIAIGTGAVASGLKSISIGVGNTVSGASSGAIGDPTDITGTGSYSLGNDNTIAADNAG
TFGNDNTLADAADGSRVIGNGNNIDVSDAFVLGNGADVTEVGGVALGSGSVSDTGADVAGYVPGGASTADQNAIEATQSTRGAVAVGN
PDAETGVYRQITGVAAGTADSDAANVAQLKSVETIAKTGWKLTTDSGSIDGIGPGDELVLKGGDGNIVISNQILSNDVSIDLADEIEV
NRVTARDPDTGASTVLDENGLSFTTQDANGEDTALGPRVTAAGIQAAGKITNVAAGEADTDAVNFSQLRQVETASGNTDQRAVKYDWT
DANTNGVIDEGELNLDSVTLAGGMGGTRISNLAPGALSAASTDAVNGSQLFGLRSRVSNVAVALGGGAAYDPVKDEWIAPKYTIGGTD
YSNVGDALAAVGGTAGAGWSLSAQGANASNVAPGETVDLRSGDGNIVVSKAETGDTVSFDLADDLDVSESITVGADPADPNAPTTVIT
GGSIVIGSTMLGSNGLVITGGPSVTTDGIDAGGMKVTNVANGTVAKDSKDAVNGGQLFDVVANATANGVGYDDKSKGTLTLEGANGTK
ITNVAAGDLNANSTDAVNGSQLYATNVKVDRLDTEVKEIDSRVTYIESFQGDLENAAVYDTDAAGKRLNTLTLEGGDPDKPVLIANVA

VKATDAVNVGQLDESVAESKSYTDEKTEWAIDQAAIYTDQVIETKVSAVNNYAQQRFAQLSGEIGQVRSEARQAAAIGLAAASLRF
EPGKLSVALGGGFWRSEGALAFGAGYTSEDGRVRANLTGAAAGGNVGVGAGLSITLN

SEQ ID NO: 16 (Bradorhizobium japonicum)

MRAFGSGNAINGTNYAAVGSNNVVAGNNGAVVGSGNGVTGDNTAAFGSSIGIAGGNNAAVGSFSTVTGSNSAAVGSFNNVSGNNSGAF
GTGQNIRGNGTFAIGDPNIVNGNNSLVFGDNNTVNGSNVAGRGDNIQLVGSNNTIAATSSAAGSSVFGSGNTVNATNAVVMGNNSTVS
GASSVAIGNGTAVTGINAIAMGTGAGANFDNSVAIGSGATTIRANQVAVGIASSTYTMSGITSAASKAAQSGFTQLNISDMAGNLATT
SLAGLGLASAGDINGINSQLAALNGRVDNLTRESRGGVALALAASSLQFDPRPGKISVSGGFGNFQGQSGLAVGLGYSYSDAMRFNAA
FTAAQQGAIGVRAGASWTLN

SEQ ID NO: 17 (Burkholderia fungorum)

MNKTYRSVWNESTGTWVAASEHASARGKKSSAKTSSTKAVVGALGLAAGLYGADAFALGGGLTLCPTTEGSAGYTAGSASSANGAYCG
SDYQWGLFSNTNADGSKSGQPIGAAIEGMNDGSLLLYGPNNIVMKNLVSMSSNKIINLAPGTVSSTSADAVNGSQLYATNQNVSNIGN
TVNNITTGAGIMYFHVNSTLADSTANGVNSIAIGGATRTDANNSISIGTGLTQASSNTGAIAIGQNASINVYGANSIAIGTNSATGGI
GGAIALGENAFATGGKMLALGSGASATTANSVALGSGSTTTANLTAAGYNPGSGTLAGTSQATNGEVSVGNAGAERRITNVAAGSAAT
DAVNVSQLQSEDAKVNTINNNVNNLSGSVTNISSTVNNITNGGGIKYFHANSTQADSSATGTDAVAIGGNAQATAANSVALGLNSTSK
GTNAIALGGAVAGGSYAFAAGSLALAATTGDIALGSSATASSANSNAYATALGTNALANATDATAIGEGASATAASSVALGARSKTTA
NLSTAGYNPGTGTLSGTTPTGEVSVGSAGKERRVTNVAAGSAATDAVNVSQLMSEDAKVNTINNNVNNLSNNVTNIAGNVTNISNTVN
NITNGGGIKYFHVNSTLADSSAGGTNSIAIGGGATTGNVTAGTSDNISIGTNATTNYGKNIAIGGNAQALGGAYDGGYNTAIGENAIA
KGDGAGGFGGGGWGQTTAIGGGSQALHDNTTAVGSGAIANVANATALGMSASATAGSAIALGQGAVASAANSVALGSGSTTTXNLSAA
GYNPGTGTLSGIASVANGEVSVGAAGKERRITNVAAGSAATDAVNVSQLQSEDAKVNTINNNVNNLSGSVTNISNTVNNITNGGGIKY
FHTKSTLADSSATGTDAVAIGGNAQATAANSVALGSNSTTTANLSAAGYNPGTGALSGIASAANGEVSVGAAGKERRITNVAAGSAAT
DAVNVSQLQSEDAKVNTISNNVNNLSGSVTNISSTVNNITNGGGIKYFHTNSTLADSTANGVNSIAIGGATRTDANNSISIGTGLTQA
SSNTGAIAIGQNASINVYGANSIAIGTNSATGGIGGAIALGENAFATGGKMLALGSGASATTANSVALGSGSTTTANLTAAGYNPGSG
TLAGTSQATNGEVSVGNAGAERRITNVAAGSAATDAVNVSQLQSEDAKVNTINNNVNNLSNNVTNIAGNVTNISNTVNNITNGGGIKY
FHTKSTLADSSATGTDAVAIGGNAQATAANSVALGSNSTTTANLSAAGYNPGTGTLSGTTPTGEVSVGSAGKERRVTNVAAGSAATDA
VNVSQLQSAIIGSTANAVAYDDGTKATVTLKGASGTKITNLTAGNLSATSTDAVNGSQLYATNQNVSNIGNTVNNITNGGGIKYFHAN
STQADSSATGSNSVAVGDRASSLGGSSVAMGDGATAVGAASIAIGNNAQNVTGSNNSVAIGGDSKAGDRSVSLGNGADTSLSSWGVAV
GTNANVSAALGTAIGAGANVSGANSTAIGANAVASATNSVALGSNSTTTANLSAAGYNPGTGTLSGIASAANGEVSVGAAGKERRVTN
VAAGSAATDAVNVSQLQSEDAKVNTINNNVNNLSGSVTNISSTVNNITNGSGIKYFHTNSTLADSSAGGANSIAIGGGAATSSSAGLS
DNMAIGTNATASYGKNIAIGGGAQATGGTYDGGYNVALGENANATAGTNAWGHNTAIGANTVINGVNSVALGISATTSGSGSMAFGSA
AQASADYAIASGAGANASAVNSVALGSNSTTTANLSAAGYNPGTGTLSGIASVANGEVSVGSAGKERRVTNVAAGSAATDAVNVSQLQ
SEDAKVNTINNNVNNLSNNVSNIAGNVTNISNTVNNITNGGGGIKYFHANSTLADSSATGTDAVAIGGNAQATAANSVALGSNSTTTA
NLSAAGYNPGTGTLSGTTPVGEVSVGSAGKERRVTNVAAGSAATDAVNVSQLQSAIIGSTANAVAYDDGTKATVTLKGASGTKITNLT
AGNLSATSTDAVNGSQLYATNQNVSNVGNTVSNLSNNVTNIAGNVTNISNTVNNITNGGGIKYFHANSTLADSSATGTDAVAIGGNAQ
ATAANSVALGSNSTTTANLSAAGYNPGTGALSATTPVGEVSVGSAGKERRVTNVAAGSAATDAVNVSQLMSEDAKVNTINNNVNNLSN
NVSNIAGNVTNISNTVNNITNGGSGIKYFHANSTLADSSATGVDAVAIGGNAQATAANSVALGSNSTTTANLSAAGYNPGTGALSGIA
SAANGEVSVGAAGKERRITNVAAGSAATDAVNVSQLQSEDAKVNTINNNVNNLSNNVSNIAGNVTNISNTVNNITNGGSGIKYFHANS
TLADSSATGTDAVAIGGNASASAANSVALGSNSTTTANLSAAGYNPGSAALSGTASAANGEVSVGAAGKERRITNVAAGSAATDAVNV
SQLQSEDAKVNAEGAATAAALGGGSTYNTTTGAITSPTYIAGGKTFNNVGDVVTNIDGRVTQNSTDITNLTTTIDNGTIGLVQQATPT
STITVAKDTGGATVDFRGTGNATRTLTGITAGELSATSTDAVNGSQLYATNQNVSNIDNTVSNLSNNVTNIAGNVTNISNTVNNITNG
GGGIKYFHANSTLADSSATGVDAVAIGGNAQATAANSVALGSNSTTTANLSAAGYNPGTGTLSGIASAANGEVSVGAAGKERRVTNVA
AGSAATDAVNVSQLQSEDAKVNTINNNVNNLSNNVSNIAGNVTNISNTVNNITNGGGGIKYFHANSTLADSSATGTNSLAAGPAAVAS
ATDAVALGNGAKATNAGAVALGAGSTTTTAVATSGTTIGGITYTFAGVAPSSTVSVGAAGSERTITNVAAGRLSATSTDAVNGSELFA
TNQQVTRNTADITNLTNNMNIGSVGLVQQDATTRTITVAKATDGTRVDFTGTGGARQLTGVAAGAVNATSVDAVNGSQLYGVSQSVAD
AIGGGSTVNTDGSISAPTYVVDGTTVHNAGDAISNLDNRVTQNTTDISTINNTLNSITTGAGVKYVHVNSTLADSLAKGAESVAIGGN
AQSQAANSVALGSNSVADRANTVSVGAAGAERQITNVAAGTADTDAVNVAQLKASGVINTDGTTNAAVTYDHNADGSANYNSVTMGNG
VAGGTTIHNVAAGSAADDAVNVSQMNAAISSVSNIIGSAGNPLFTADGNRDTEAAVASGTHATAMGANAKASAANSVALGANSVADRE
NTVSVGSAGNERQVTNVAAGTATTDAVNVGQLNQAIGASIGNLPAGMSAKDYTDQQINAVQNGVNQVAKNAYAGIAAATALTMIPDVD
QGKTIAVGVGGGSYKGSQAVALGISARITQNLKMKAGAGTSSQGTTVGLGASYQW

SEQ ID NO: 18 (EPEC)

MLIQQNSEVINQLAGNTSETYIEENGASINYVRTNDTGLTFTDASAAGIGSTAVGYNTVAKGDNSVAMGYNSFAEGHSSVAIGQGSYS
GVETSIALGSESVSSRVIVKGSRNTSVSEEGVVIGYDTTDGELLGALSIGDDGKYRQIINVADGSEAHDAVTVRQLQNAIGAVATTPT
KYYHANSTAEDSLAVGEDSLAMGAKTIVNGNAGIGIGLNTLVLADAINGIAIGSNARANHADSIAMGNGSQTTRGAQTNYTAYNMDAP
QNSVGEFSVGSEDGQRQITNVAAGSADTDAVNVGQLKVTDAQVSQNTQSITNLNTQVTNLDTRVTNIENGIGDIVTTGSTKYFKTNTD

DANAQGKDSVAIGSGSIAAADNSVALGTGSVANEENTISVGSSTNQRRITNVAAGVNATDAVNVSQLKSSEAGGVRYDTKADGSID
NITLGGGNGGTTRISNVSAGVNNNDAVNYAQLKQSVQETKQYTDQRMVEMDNKLSKTESKLSGGIASAMAMTGLPQAYTPGASMAS
IGGGTYNGESAVALGVSMVSANGRWVYKLQGSTNSQGEYSAALGAGIQW

SEQ ID NO: 19

GSGGGG

SEQ ID NO: 20 (Haemophilus aegyptius)

GTACCGCACGAGCTGGCAAAAAAGGCACGGCAGTCTCTTTTGTCGAAGCCCATGATTACAAGTTGCTAGGTAAAATCAAACGTTATAC
TGAGGAAATTTTAAAGGCACGCATTTTAGCAGGTTTAGAACCTCGCACTAAGCCACCAAAAGATGGCGAAGTGAAATCTGTCAGCAAA
AAACAAAAGGCGCGCATTAAAGAAAAACGTGAAGATAAGAAAAAAACAGAGGCAAAGAAAAAAGTAAAATTGCGTCATAAGGATACAA
AAAATATCGGCAAACGACGCAAGCCAAGTAATAGTAATATTTAATTAGGTATGATGTAAATTCTGCTTGAGGCAAATTTTACATAGGA
AATTTTTCTATATTGCTTTAACGTTTTTTTATAGTAGAAGTATATACTCAGTTATGGTTATGGTTACATAGTATAGTTTTACTTTGTT
CTAGTTCACTTTAATAACCTTAAATAATTGAGGATTTCTTATGAAAAGAAATTTATTAAAACAATCTGTAATCGCTGTGTTGATAGGT
GGCACTACTGTTTCTAATTATGCTTTAGCACAAGCACAAGCACAAGCACAAGTCAAAAAAGATGAACTTAGTGAGTTAAAGAAACAAG
TAAAGGAAATGGATGCTGCTATCGATGGTATTCTTGATGATAATATTGCTTATGAAGCTGAAGTTGATGCAAAACTTGATCAGCATTC
TGCTGCTCTTGGTAGACATACAAATAGACTCAATAATCTTAAAACGATTGCAGAGAAAGCAAAAGGTGATTCAAGTGAAGCACTTGAT
AAAATTGAAGCTCTTGAAGAACAAAATGATGAGTTTTTAGCGGATATTACAGCTTTAGAAGAGGGAGTTGATGGTTTAGATGATGATA
TCGCAGGTATTCAAGATAATATTTCTGATATAGAAGATGATATTAATCAAAATTCTGCAGACATCGCAACTAACACAGCGGCAATCGC
AACTCACACTCAACGTCTTGATAATTTAGATAACAGAGTAAATAACCTTAATAAAGATCTTAAACGTGGTCTTGCTGCTCAAGCTGCA
TTAAATGGTTTATTCCAACCGTATAACGTAGGTAAATTAAATCTTACTGCTGCTGTAGGTGGTTATAAATCTCAAACTGCAGTTGCTG
TAGGTAC

***SEQ ID NO: 21* (Haemophilus somnus)**

ATGAAAAAAGTACAATTTTTTAAATATTCATCATTGGCATTAGCATTGGGTTTAGGGGTAAGTGCTTCTGCTTTGGCAGCCCCAACAA
GTACAAGTACGACTACTGGACCAGAGGCGCCTCCTACAGGCCCTGCTCCTACGGCGAAAGACCCTCTAGCAGAAACAGCGTTAGCCTA
TGATTTGGAGAACGAAGTTGCGTATCTTCGTATGAAGGCGGGTGAGTGGATGCAATTGGGGCTTGATCCTGAAAAAGAAGTCATCAAA
GGCTGGAATGAGGTAAAATCTCTCCCTCGTATCGATGGAAATGGAAAGGATAAACAGACAAAAGATCAAATAGCAATGTTGATAAGAA
CGGTTGATAATACAAAAGAGCTTGGTCGGATCGTTAGTACAAACATTGAAGATATTAAGAACCTTAAAAAAGAGCTTTACGGTTTTGT
AGAAGATGTGAACGAGAGTGAAGCACGCAATATCTCAAGAATAGATGAGAATGAGAAAGATATTAAGAACCTTAAAAAAGAGCTTTAC
GATTTTGTAGAAGATGTGAACGAGAGTGAAGCACGCAATATCTCAAGAATAGATGAAAATGAGAAGGACATTAATACTCTTAAAGAGC
TAATGGATGAGGATTTAAATTCAGTCTTAACCCAAATTGAAGATGTAAAACTCACATTTCAAGATGTCAATGATAACGTTAATTTGGC
ATTTGAAGAGATTAATGGAAATGCCCAAAAGTTTGACACTGCTATTGAAGGACTTACTTCAGGTTTGAGCGATTTACAAGCTAAAGTC
GATGCAAATAAACAAGAAACTGAAGACGATATTGCGGACAATGCCAAGGCTATTCATAGCAACACAAAAGGTATTGCTAAAAATACCA
AGGATATTCGTGACTTGGACACCAAAACCAAGCAAATGTTGGAAAATGACAAAAACTTGATGACCGGTTTAGAATCTTTAGCAACAGA
AACAAGCAAAGGCTTTGAAAGATTTGATGTCAAAACACAACAATTAGATCAAGCCGTCGCAAATGTCGTCGGTCGAGTAGACATAACT
GAGCAAGCTATTCGCCAAAACACTGCAGGCTTAGTCAATGTGAATAAACGTGTCGATACACTCGACAAAAACACCAAAGCCGGTATCG
CTTCTGCAGTCGCTTTAGGTATGTTGCCACAATCCACTGCTCCGGGTAAATCATTAGTGAGCTTAGGTGTCGGTCATCACCGTGGGCA
AAGTGCTACTGCTATTGGAGTATCTTCTATGAGCAGTAACGGTAAATGGGTTGTTAAAGGCGGTATGAGCTATGATACACAGCGTCAT
GCTACTTTCGGCGGTTCTGTCGGTTTTTTCTTTAACTAA

SEQ ID NO: 22 (Escherichia coli)

ATGAAAACTGTAAACGTAGCTTTACTGGCACTCATAATTTCAGCAACATCCAGCCCTGTTGTTTTAGCTGGTGATACCATTGAAGCGG
CGGCAACAGAGCTTTCAGCCATTAACTCTGGCATGTCGCAATCGGAGATTGAGCAGAAGATTACCCGCTTTTTAGAACGCACAGACAA
CAGCCCCGCTGCGTATACCTATTTGACTGAACATCACTACATCCCTTCTGAAACACCTGATACCACTCAGACTCCCACTGTCCAGACA
GATCCTGACGCAGGACAAAAAACCGTTGCCGCTACAGGTGATGTACAGACAACTGCCCGTTATCAGAGCATGATCAACGCCCGACAGT
CTGCGGTAACTGACGCCCAGCAAACGCAAATTACAGAGCAACAGGCGCAGATCGTAGCCACACAAAAAACGCTCGCCGCGACTGGAGA
TACGCAAAATACCGCGCATTATCAGGAAATGATTAATGCCAGACTGGCGGCTCAAAATGAGGCTAATCAGCGCACCGCCACTGAACAA
GGGCAGAAAATGAATGCGCTGACAACCGATGTGGCAGTACAACAGCAAAATGAAAGGACTCAATACGATAAACAAATGCAAAGTCTGG
CGCAGGAGTCTGCCCAGGCACATGAACAAATTGACAGCCTGTCACAAGACGTAACCCAAACGCACCAACAGTTAACCAACACCCAAAA
ACGGGTTGCAGATAACAGCCAGCAAATTAACACGCTCAATAACCATTTCAGTTCGCTAAAAAACGAAGTTGATGACAATCGTAAAGAA
GCCAATGCGGGAACTGCATCTGCCATCGCTATCGCCTCACAACCACAGGTTAAAACCGGTGACGTGATGATGGTGTCAGCGGGAGCGG
GAACCTTCAACGGTGAATCTGCGGTGTCTGTCGGAACATCATTTAATGCCGGAACGCATACGGTACTTAAAGCCGGTATTTCTGCGGA
TACACAATCTGATTTCGGCGCAGGTGTCGGCGTGGGATATTCGTTCTAA

SEQ ID NO: 23 (Escherichia coli)

ATCGCCAAACAGCGTCGGCGTCTGGGCGCAGTAAGAGACTTGCTGACGGTAGATTTCTGGCTTTAGTGTGCTGACATCCTCACCTTCA
AACAGTAACGTTCCGCTGGTTGGGCTGATCAATGAAGCAACTATTTTTAGCAGCGTACTTTTGCCACAACCAGAAGGACCGGTAATTA
ACTTAAATTCGCCAGCACGCAGCGAAAAATTGATGTTATTAAGAATCTTCGCATCACCCGCCAGATATCCTACGTTTTGTAGCTGAAG
CAAAGGACTATTTTCCTGCATCGCTGTTCCCTTTTTCTGATTTTTACTAAAAACAGTTTATCCTTCGCAGGAATAAGGGGGAACTCTC
TTTCAGTAATCAGGTAAAATTGTTTAAAAATGCTTTTTGC[illegible]CCGTACAACAGGAGGTTTTTCCGATGCTTATCT
TTATCCCGATTCTCATTTTTGTCGCGCTGGTCATTGTCGGCGCGGGCGTCAAAATCGTGCCGCAGGGCTATCAATGGACGGTAGAACG
TTTTGGTCGCTATACCAAAACGTTACAGCCGGGGCTCAGTCTGGTGGTGCCGTTTATGGATCGCATTGGTCGCAAGATCAATATGATG
GAGCAAGTGCTCGATATCCCTTCCCAGGAAGTTATCTCGAAAGATAACGCCAACGTTACCATCGACGCAGTCTGTTTTATTCAGGTGA
TTGACGCGCCACGCGCGGCTTATGAAGTCAGCAATCTGGAGCTGGCGATCATCAACCTGACCATGACTAACATCCGTACCGTGTTGGG
TTCAATGGAACTTGACGAAATGCTCTCTCAGCGCGACAGCATCAACTCACGCCTGCTGCGTATTGTCGATGAGGCCACCAACCCGTGG
GGGATTAAAGTCACCCGTATTGAAATTCGCGACGTGCGCCCACCGGCAGAGCTTATCTCTTCAATGAACGCGCAGATGAAAGCGGAAC
GTACCAAACGCGCTTACATTCTTGAAGCGGAAGGGATCCGTCAGGCGGAAATCCTCAAAGCCGAAGGTGAAAAACAGTCGCAAATCCT
GAAAGCGGAAGGCGAACGTCAGTCGGCGTTTTTACAGGCTGAAGCGCGTGAACGTTCCGCTGAAGCAGAAGCCCGCGCCACCAAAATG
GTGTCTGAAGCCATCGCCTCCGGTGATATTCAGGCGGTGAACTACTTCGTAGCGCAGAAATACACCGAAGCGTTACAGCAGATCGGTT
CCTCCAGTAACAGCAAAGTAGTGATGATGCCATTAGAGGCCAGCAGCCTGATGGGGTCGATTGCCGGGATTGCCGAGCTGGTGAAAGA
CAGCGCCAACAAGCGGACTCAGCCATGATGGAGTTAATAGTCGTTCATCCACATATTTTCTGGCTCAGTCTCGGCGGTTTGCTGCTGG
CAGCCGAGATGCTGGGCGGAAATGGTTATTTGTTGTGGAGTGGCGTGGCAGCAGTGATTACTGGCCTGGTGGTCTGGCTGGTGCCGCT
GGGTTGGGAGTGGCAAGGGGTGATGTTTGCCGTCCTGACGCTGCTCGCCGCCTGGCTGTGGTGGAAATGGTTGTCGCGGCGGGTGCGC
GAACAAAAGCACAGCGACAGTCATTTAAACCAGCGCGGGCAGCAGCTGATTGGCCGACGTTTTGTGCTGGAATCTCCGCTGGTCAACG
GGCGCGGTCATATGCGCGTCGGTGACAGTTCATGGCCTGTCAGCGCCAGCGAGGATCTCGGCGCAGGTACGCATGTTGAAGTCATTGC
GATAGAAGGGATAACGCTGATCATCCGTGCGGTCATCGCCTGATGCGACGCTGACGCGTCTTATCATGCCCGGAAGTCTGCGCCCGAA
TCGTAGGCCGGATAAGGCGTTTACGCCGCATCCGGCAGTCGTGCACCGACGCCTGATGCGACGCGGGCGCGTCATATCACGCCAAAAC
CGTAGGCCGCCTCCGCCATGTTAAATGTTAACTGGCATTGGCAATTTACTCTTCCCGGCCTTTACTCATACTTTTTTGGTCTTCATCC
GGATAGTGTTTTTTTAGATATTCCAGGACGTTTTTATTGACCTTGTGTTGCGTATACACCCACCCTTTCCAGTAATCAGGCTGGTCCA
GGTAAACTTCTGGCGGAATGGTGAAATCAGAAAGCGTTAACCATTCGGCTAACAGATCGGGGTTTCGTTTCTGTATCAACTGCAACAG
CATAATCAGCGACATGGCAGAGGCAGGAGCCGTACTATCGCCGCTTAAATACTTCCACACTGTCGACCGGTTCGAACGAAAAAGGATC
GGTAGCAATGCCCGGTCCAGATTCATTTCATTAAAAATCTTCTCAAATTCATTCATTTAAATTTTCCTGCCTGGCGTAAACCTCTTAA
AAATTGAGATTTATCAAAGAAACGCATTTTAGCACACATCAGGAACCGCTTCACGTTTAGTCCAGAAACAGAATTTATTTCGCTTATC
AAAACAAGTCTTTACTCTTTTTTACATTGAAAGAGCACGAAATGATTTCCTTTTTTATTTATATAAGAAACCATTTTTGTTTCTTATT
GATGGTGTTTACGCTTACAACAGACAAAAATGCGCTTTACATCACACAAATGGCGGCGTAGATTTCGATTAAATTGCAACGCAGTTTA
TTTCTTAAAACAATATTATTTGTTTCTTATAGAAACATTAATACGACTTATTTTGAACAAGAGAAAATGAATGAAAACTGTAAACGTA
GCTTTACTGGCACTCATAATTTCAGCAACATCCAGCCCTGTTGTTTTAGCTGGTGATACCATTGAAGCGGCGGCAACAGAGCTTTCAG
CCATTAACTCTGGCATGTCGCAATCGGAGATTGAGCAGAAGATTACCCGCTTTTTAGAACGCACAGACAACAGCCCCGCTGCGTATAC
CTATTTGACTGAACATCACTACATCCCTTCTGAAACACCTGATACCACTCAGACTCCCACTGTCCAGACAGATCCTGACGCAGGACAA
AAAACCGTTGCCGCTACAGGTGATGTACAGACAACTGCCCGTTATCAGAGCATGATCAACGCCCGACAGTCTGCGGTAACTGACGCCC
AGCAAACGCAAATTACAGAGCAACAGGCGCAGATCGTAGCCACACAAAAAACGCTCGCCGCGACTGGAGATACGCAAAATACCGCGCA
TTATCAGGAAATGATTAATGCCAGACTGGCGGCTCAAAATGAGGCTAATCAGCGCACCGCCACTGAACAAGGGCAGAAAATGAATGCG
CTGACAACCGATGTGGCAGTACAACAGCAAAATGAAAGGACTCAATACGATAAACAAATGCAAAGTCTGGCGCAGGAGTCTGCCCAGG
CACATGAACAAATTCACAGCCTGTCACAAGACGTAACCCAAACGCACCAACAGTTAACCAACACCCAAAAACGGGTTGCAGATAACAG
CCAGCAAATTAACACGCTCAATAACCATTTCAGTTCGCTAAAAAACGAAGTTGATGACAATCGTAAAGAAGCCAATGCGGGAACTGCA
TCTGCCATCGCTATCGCCTCACAACCACAGGTTAAAACCGGTGACGTGATGATGGTGTCAGCGGGAGCGGGAACCTTCAACGGTGAAT
CTGCGGTGTCTGTCGGAACATCATTTAATGCCGGAACGCATACGGTACTTAAAGCCGGTATTTCTGCGGATACACAATCTGATTTCGG
CGCAGGTGTCGGCGTGGGATATTCGTTCTAATATTTCAATCCTCAATATAAATAAGAGCAAGGAAGCTTGCCGGGTTCACCTCTTCAT
TAATTTGTACATTATTTAAGGTTAACAATGATGAATAGCTCCATTAAATCGTTTTCCCTGCTGGCGGTTATATTACTGGCTGGCTGTA
GTTCACCCACTTCCCGCATCGCAGATTGCCAGGCGCAGGGCGTCAGTCATGACACCTGTTACCTCGCAGAACAGCAGCGTCAGGCGGC
TATTTTAAGTGCATCCGAGGCACAGGCATTTAAAAATGCAGAAGCCGCACAACACGCCCAGGCGGCAAAGAAAGCCATTTATAAAGGA
TTTGGCATGACCTTTAGAATGAGCAGTAAAAACTTTGCTTATCTCAATGATTCATTATGTGCAATTGATGAAGACAATAAAGATGCCA
CTGTTTATCAGTCAGGTCTATATAACGTCATTGTTTATCATCACACAGGAAAAGTCGCCTTAATGAAAGAAGGCCAGTTTGTGGGTTA
TTTAAAATGAAGGAGCAAAGGAAAATACCCCTGACGCATATTATGATTATCGGTGCGTTTATTTTTGCCTTCTTGCAAGTAGTATTAT
TAGCCTCCCTGGTTCACGCTGTGAATGTTAACAACGAAATCCAGGAAGGCTTATTTCAGTCGGGGCGCATTATGGTAGAAAGTTTGCA
GCATATTCTTTCGGTGCAAACGGGGATTCACTGATTTTCACCCCGCCCGATGATGACAGCAGCCGGAGAGATTTTCGATAATCGGGCA
GTCGGCGCTGTCATCACCGGGGCAGGCATTCGCCAGCGCCAGTAGCTGGTTGCGCATAGATTGCAGTTCTTCGATATGCCGTTCAATC
TCCGCCACCTTCTCCAGCGTGCGACGTTTGACGTCGGCACTGTGACGCTGCGGGTCGTTAAACAGATTCACCAGCTCGCCGCTCTCTT
CCAGGTTAAAGCCCACCTGGCGCGCCTGGCGCAGTAAGGTCAATTCGTTGAGATGCTGCTGCGTGTAGGTTCGATAACCATTTTCGCT

GGCATCGGCGGCGTCACCAGCCCCTTCTCTTCATAGAAGCGAATGGCTTTGCTGGTCAGGCCGGTAATTTTTGCTACATCGCTAATG
TCATCGTTCGCGCAACGCC

SEQ ID NO: 24 (EPEC)

ATGAAAACTGTAAACGTAGCTTTACTGGCACTCATAATTTCAGCAACATCCAGCCCTTTTGTTTTAGCTGGTGATACCATTGAAGCGG
CGGCAACAGAGCTTTCAGCCATTAACTCGGGCATGTCGCAATCGGAGATTGAGCAGAAGATTACCCGCTTTTTAGAACGCACCGACAA
[illegible]
GATCCTGACGCAGGACAAAAAACCGTTCCCGCTACAGGTGATGTACAGACAACCGCCCGTTATCAGAGCATGATCAACGCCCGACAGT
CTACGGTAACTGATGCCCAGCAAACGCAAATTACAGAGCAACAGGCGCAGATCGTAGCCACACAAAAAACGCTCGCCGCGACTGGAGA
TACGCAAAATACCGCGCATTATCAGGAGATGATTAATGCCAGGCTGGCGGCTCAAAATGAGGCTAATCAGCGCACTACCACGGAACAA
GGGCAGAAAATGAATGCACTGACAACCGATGTGGCAGCACAACAGCAAAAAGAAAGGGCTCAATACGATAAACAAATGCAAAGTCTGG
CGCAGAAGTCTGTCCAGGCACATGAGCAAATTGAAAGTCTGAGACAAGATTCCGCACAAACGCAGCAACAGTTAACCAACACCCAAAA
ACGGGTTGCAGATAACAGCCAGCAAATTAACACGCTCAATAACCATTTCAGTTCGCTAAAAAACGAAGTTGAGGACAATCGTAAAGAA
GCCAATGCGGGAACTGCATCTGCCATCGCTATCGCCTCACAACCACAGGTGAAAACCGGTGACTTGATGATGGTCTCAGCGGGAGCGG
GAACCTTTAACGGTGAATCTGCGGTGTCTGTCGGAACATCTTTTAATGCCGGAACGCATACGGTACTTAAAGCAGGTATTTCTGCGGA
TACACAATCTGATTTCGGTGCGGGTGTCGGCGTGGGATATTCGTTCTAA

SEQ ID NO: 25 (EAEC)

ATGAAAACTGTAAAGCTGTCTTTACTGGCTGTCGTTGTTGCTACCGCGGTAAGTCCATCTGCGTTTGCGGGTGATACTGTTGAGGCGG
CAACGACAGAATTAACGGTAATCCAGCCAGGAATGTCGCAATCGGAAATTGATCAGAAAATTGGTCGATTTTTAGAAAGGACAGGGAA
TAGTGTAGCCGCACAAAATTATCTGATTGCGCATGATTACCAGACAACGACGCCTCAGGAAAATACAGCTGCTTCTCCCGTACAGCCC
ACCAATACGCTGAACCCGATAACCAATCAAGCGCAGACCGACCGCGACAACGGGCAGGATACCGCCATTCAGGACGCGCAGCACGCCG
CCAACTGGGCTTCACTGAAAGCTGATGACGCGCAGCACGCCATCACGGTGGCGCAGACGGATATTGATGCCAATACAGCCGCCATCAC
CGATACCCGTAATGATGTCTCCGCAGTGCAGTCAGACGTCACCAACATAAAAGGCGATGTCGCACATGCCCAGTCAACGGCTGACCAT
GCCAACGCTAACGCCAACACCGCTCTGATTAACGGCGTCAAACTTTCCGGTGCTGTGACAGAAAACAAAAACAACATCGAACAGAACC
GCAGCGATATTGCTGACCAGCAGAAACTGTTGGCATCAAACGAGCAAAAACAGATCGTCCGCGACAACGGGCAGGATACCGCCATTCA
GGACGCACAACATGCCGCCAACTGGGCTTCACTGAAAGCTGATGACGCGCAACACGCCATCACGGTGGCGCAGACGGATATTGATGCC
AATAAAGCCGCCATCACCGACATCCGTAATGATGTCTCCGCAGTGCAGTCAGACGTCACCAACATAAAAGGCGATGTCGCACATGCCC
AGTCAACGGCTGACCATGCCAACGCTAACGCCAACACCGCTCTGATGAACGGCGTCAAACTCTCCTCTGCTGTGACAGAAAACAAAAA
TAATATCGAACAGAACCGCAGCGATATTGCTGACCAGCAGAAACTGTTGGCATCAAACGAGCAAAAACAGATCGTCCGCGACAACGGG
CAGGATACCGCCATTCAGGACGCACAACATGCCGCCAACTGGGCTTCAATGAAAGCTGATGACGCGCAGCACGCCATCACGGTGGCGC
AGACGGATATTGATGCCAATAAAGCCGCCATCGCCGACACCCGTAATGATGTCTCCGCAGTGCAGTCAGACGTCACCAACATAAAAGG
CGATGTCGCACATGCCCAGTCAACGGCTGACCATGCCAACGCTAACGCCAACACCGCTCTGATTAACGGCGTCAAACTTTCCGGTGCT
GTGACAGAAAACAAAAATAATATCGAACAGAACCGCAGCGATATTGCTGACCAACAGCAACAACTCGACGAAACCCGGAAAATCGTTG
CCGCCACCGGGGATGTGCAGACTGCCGCCCGATATCAGAGCATGATTGACGCCAGACAGACAGCCGCTGCCAATGCGCAACAGGCACA
AGCTGACACCCAGCAGCAACAAATGGACGATCAGCAGAAACAAATCGACGCGACGCAAAAAACGGTTTCCGCACTTGGCGATGCCCAG
ACCAACGCACATTATCAAGAGATGGTTAACGCCGGACTGAGAGCACAAAATGATGCGAATGCGCGTACTGCAGCAGAACAAAAACAAA
AAATAGATACTCTGGCGACTAACCAGGCAACGCAACAGCATATCAATAGTGTGCAGTACGGGGAACAAATTCAGCGTCTGGCGCAAGA
CTCAACACAAACGCATGAACAAATTGACAGCCTGACACAAGACGTAACCCAAACGCATCAGCAGTTAAGCAACACGCAAAAACGAGTA
GCGGATAATAGCCAGCAGATTACTACGCTCAATAACCATTTCAGTTCGCTGAAAAACGAAGTTGAGGACAACCGTAAAGAAGCCAATG
CGGGAACTGCATCAGCCATCGCTATCGCCTCACAACCACAGGTGAAAGCCGGTGACTTTATGATGATGTCAGCGGGAGCGGGAACCTT
CAACGGTGAATCTGCGGTGTCTGTCGGAACATCTTTTAATGCCGGAACGCATACCGTGATTAAAGCCGGTGTCTCTGCGGATACGCAA
TCTGATTTCGGCGCGGGTGTCGGCGTGGGATATTCTTTCTAA

SEQ ID NO: 26 (UPEC)

ATGAACAAAATATTTAAAGTTATCTGGAATCCGGCAACAGGCAGTTACACCGTTGCCAGCGAAACGGCGAAGAGCCGTGGTAAAAAAA
GCGGGCGCAGTAAGCTGTTAATTTCTGCACTGGTTGCGGGTGGGTTGTTGTCGTCGTTTGGGGCAAGTGCAGATAATTACACTGGGCA
GCCAACTGATTATGGCGATGGCTCAGCAGGTGACGGCTGGGTTGCTATCGGTAAAGGGGCAAAAGCAAATACCTTTATGAACACTAGT
GGCGCGAGTACAGCTTTAGGATATGACGCGATAGCCGAAGGTGAGTACAGTTCTGCCATCGGGTCAAAAACCCTTGCAACTGGTGGAG
CATCCATGGCGTTCGGGGTTAGTGCAAAAGCAATGGGTGACAGAAGTGTCGCGCTAGGTGCATCGTCAGTAGCAAATGGCGATCGTTC
GATGGCTTTTGGTCGTTACGCAAAGACGAATGGTTTTACATCTCTTGCTATTGGGGACTCCTCCCTTGCCGATGGTGAAAAAACTATT
GCGTTAGGAAATACGGCTAAAGCTTACGAAATTATGAGCATCGCCCTCGGTGATAATGCCAATGCGTCAAAAGAGTATGCAATGGCGC
TGGGAGCAAGTAGCAAAGCTGGCGGTGCTGATAGCCTCGCATTCGGCAGAAAATCTACAGCTAATAGCACTGGCTCACTGGCAATAGG
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SEQ ID NO: 29 **(Burkholderia fungorum)**

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SEQ ID NO: 30 (EPEC)

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***SEQ ID NO: 31* (Shigella)**

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[illegible]GCCCTGAATGCTATCGATACCACTCCTGACGACGCTCTGCTCTGGGATGCC[illegible]
[illegible]CAGTGTAATCACTAACGTCGCTAACGG[illegible]
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CACCGCCTACAACATGGACGCACCGCAGAACTCTGTAGGTGAGTTTTCTGTCGGTAGTGAAGACGGTCAACGTCAGATCACAAACGTC
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CAAGTACTTCAAGACCAACACCGATGGCGTAGATGCCAACGCCCAGGGTAAAGATAGCGTTGCTATTGGTTCTGGTTCCATTGCTGCC
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***SEQ ID NO: 32* (Brucella melitensis)**

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SEQ ID NO: 33 ([illegible])

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AATGCCAAAGGTGTTGCCGACAATAGGGCTGCCATCAGCCAAAACCGCGGTCGCATCAATGCTAACGCAGCAGGTGTTGCTAGCAATA
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SEQ ID NO: 34 **(Ralstonia solanacearum)**

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SEQ ID NO: 35 **(Sinorhizobium meliloti)**

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SEQ ID NO: 36 **(Bradorhizobium japonicum)**

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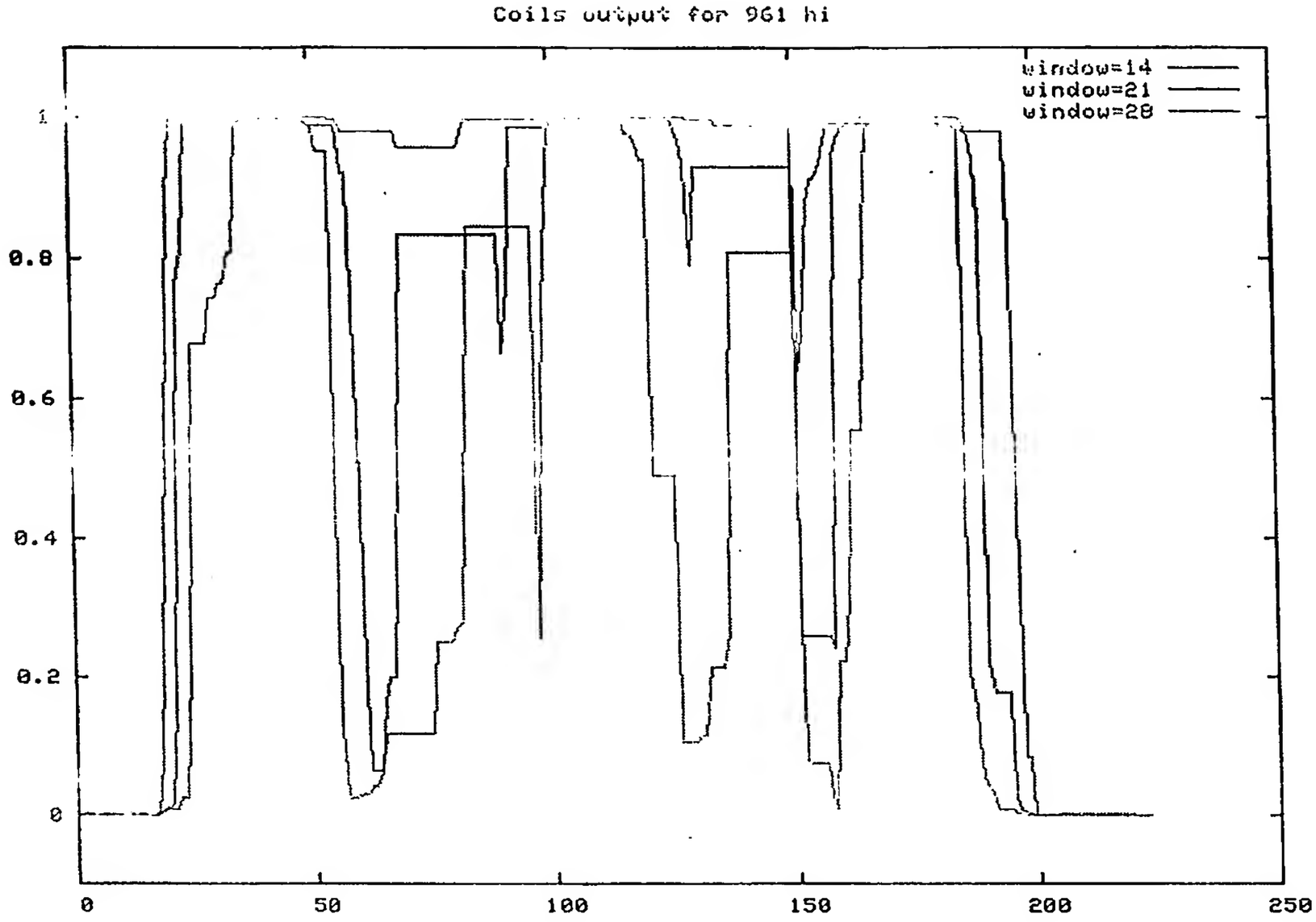
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200
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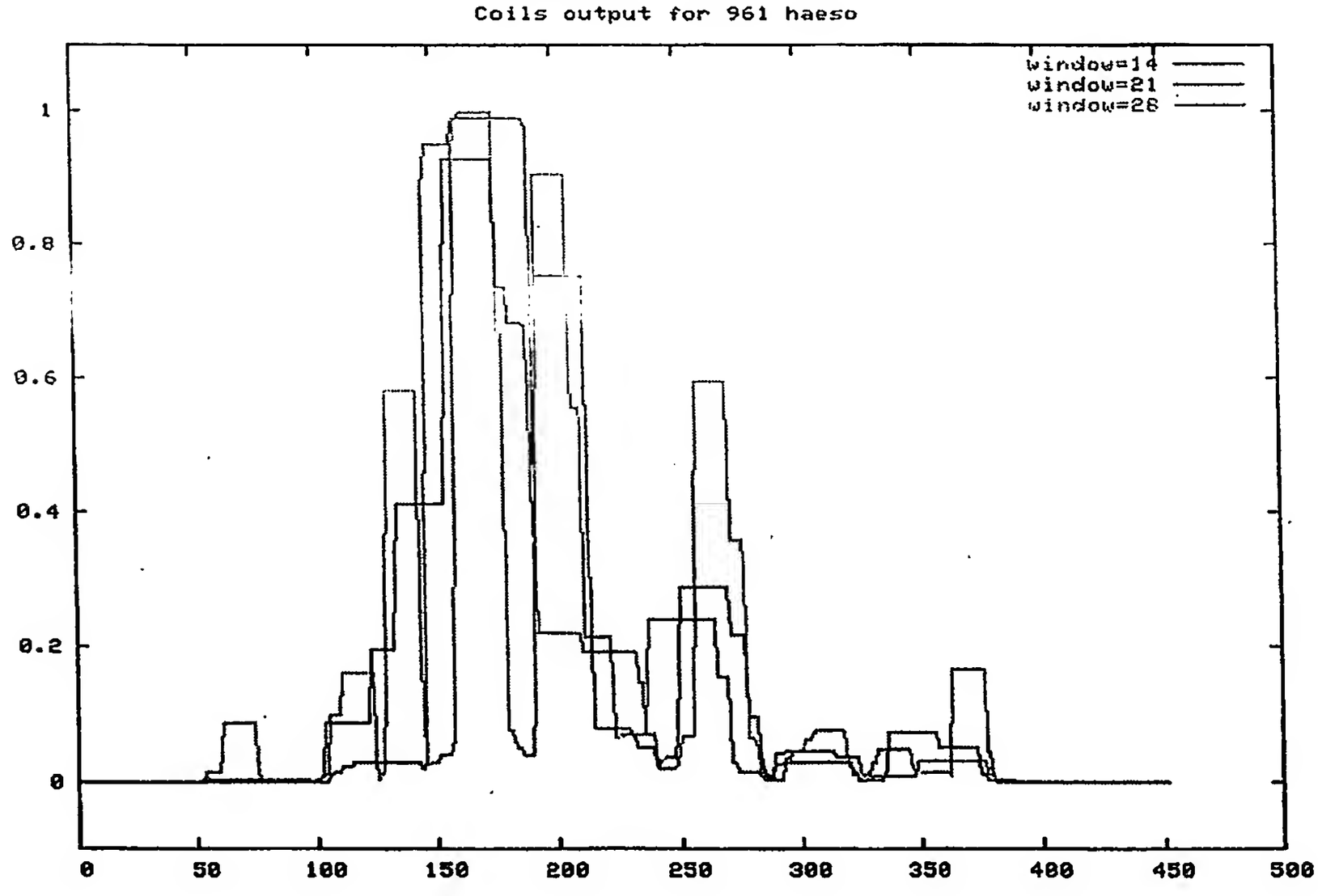
FIGURE 2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300
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450
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FIGURE 3

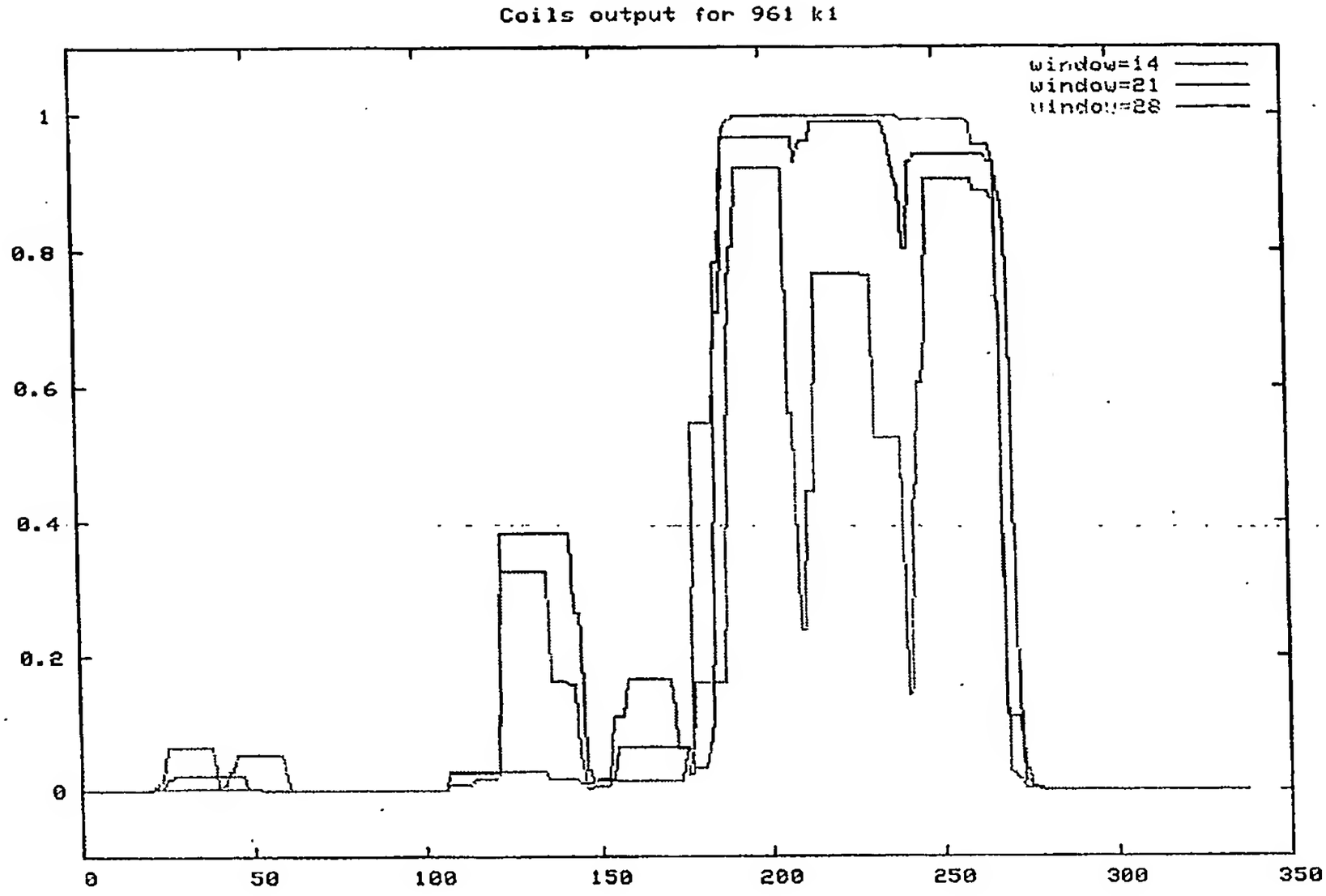

FIGURE 4

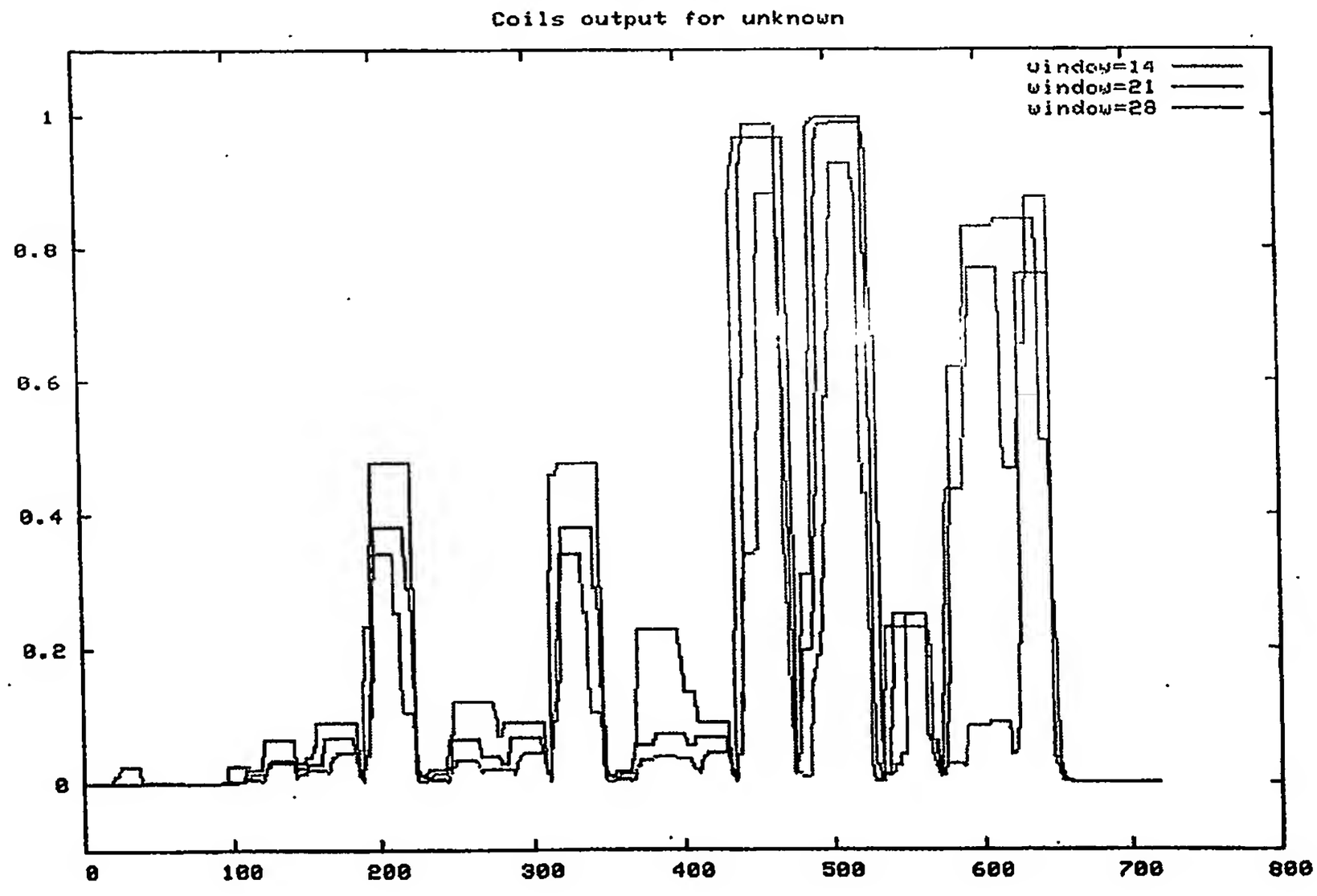

FIGURE 5

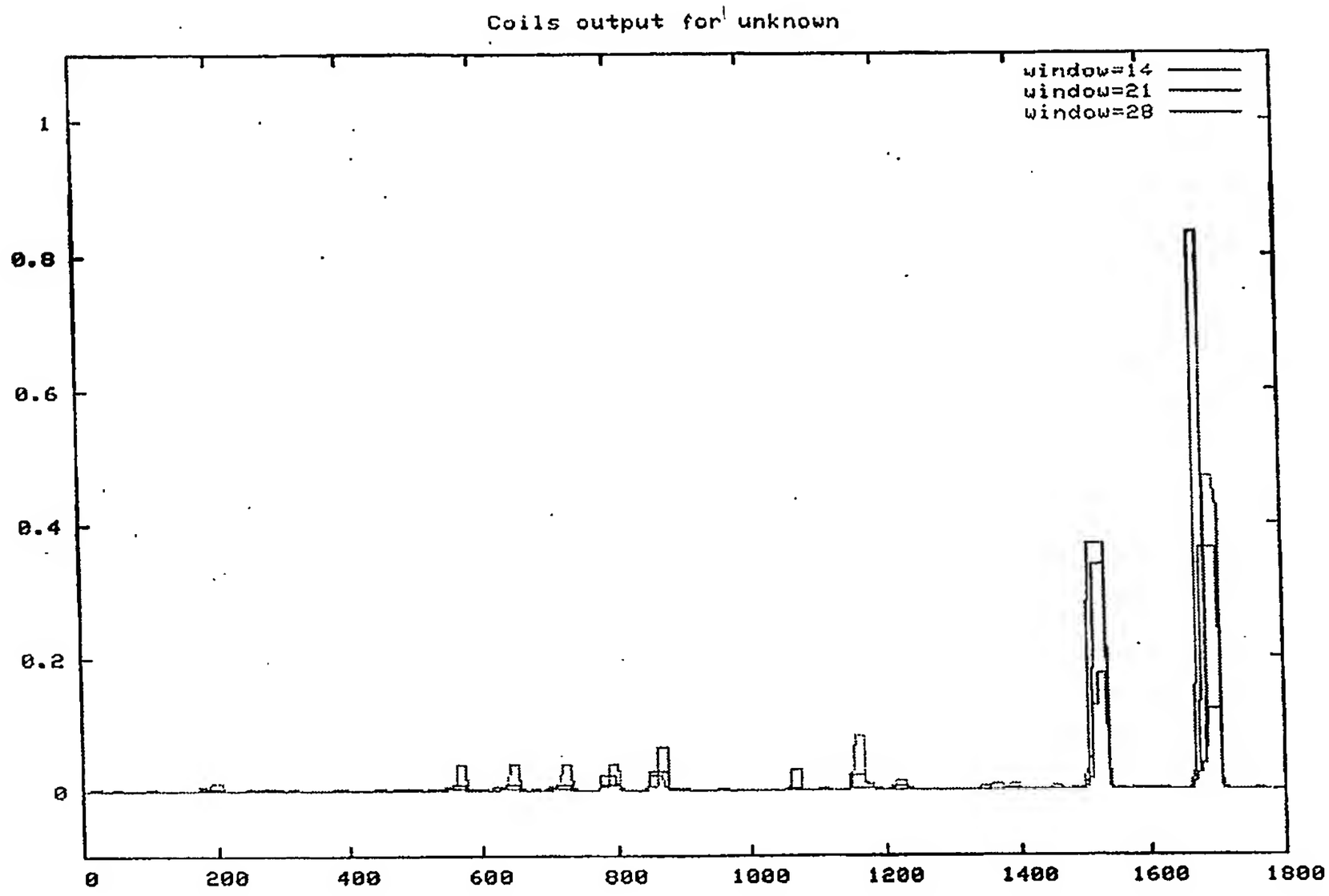

FIGURE 6

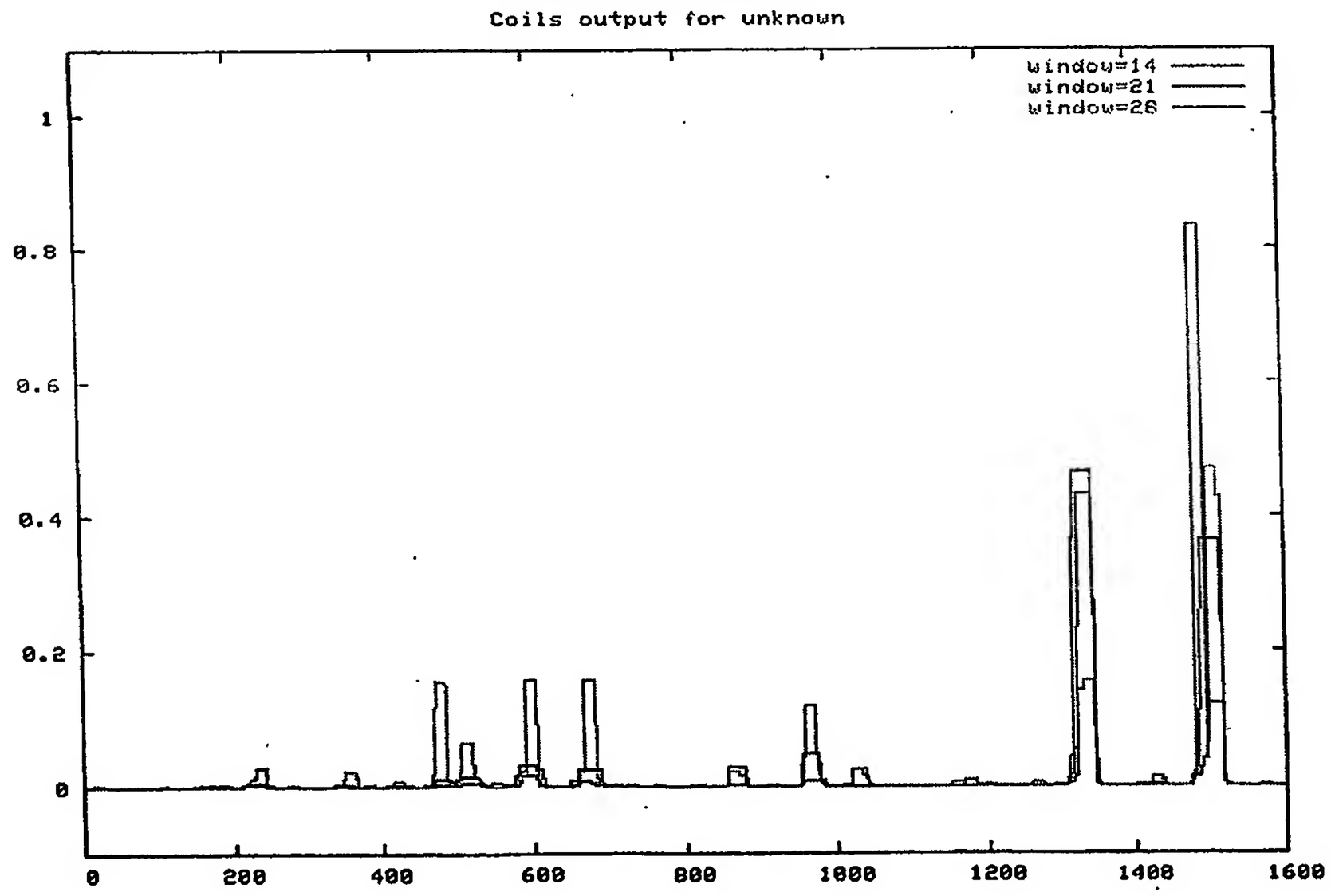

FIGURE 7

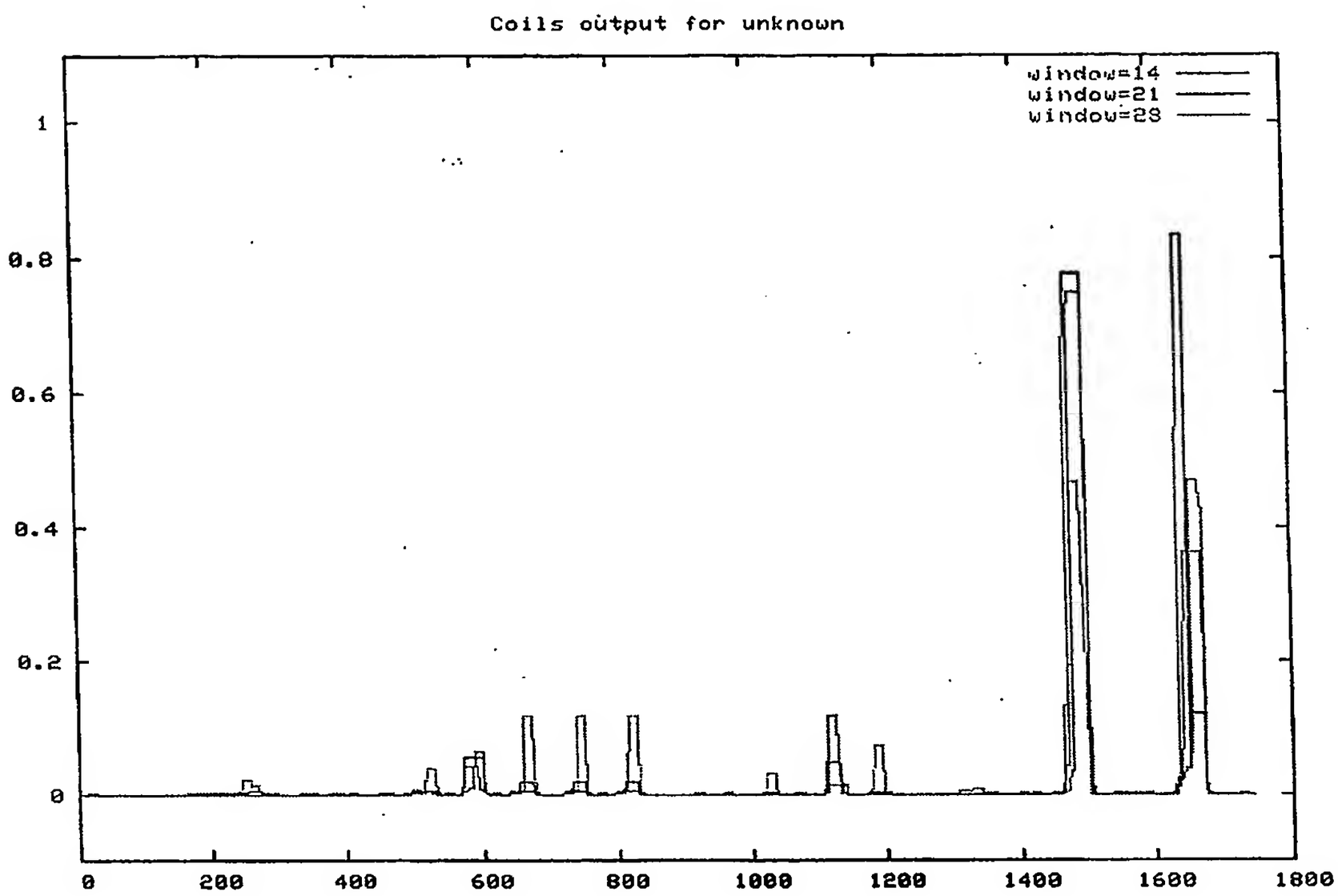

FIGURE 8

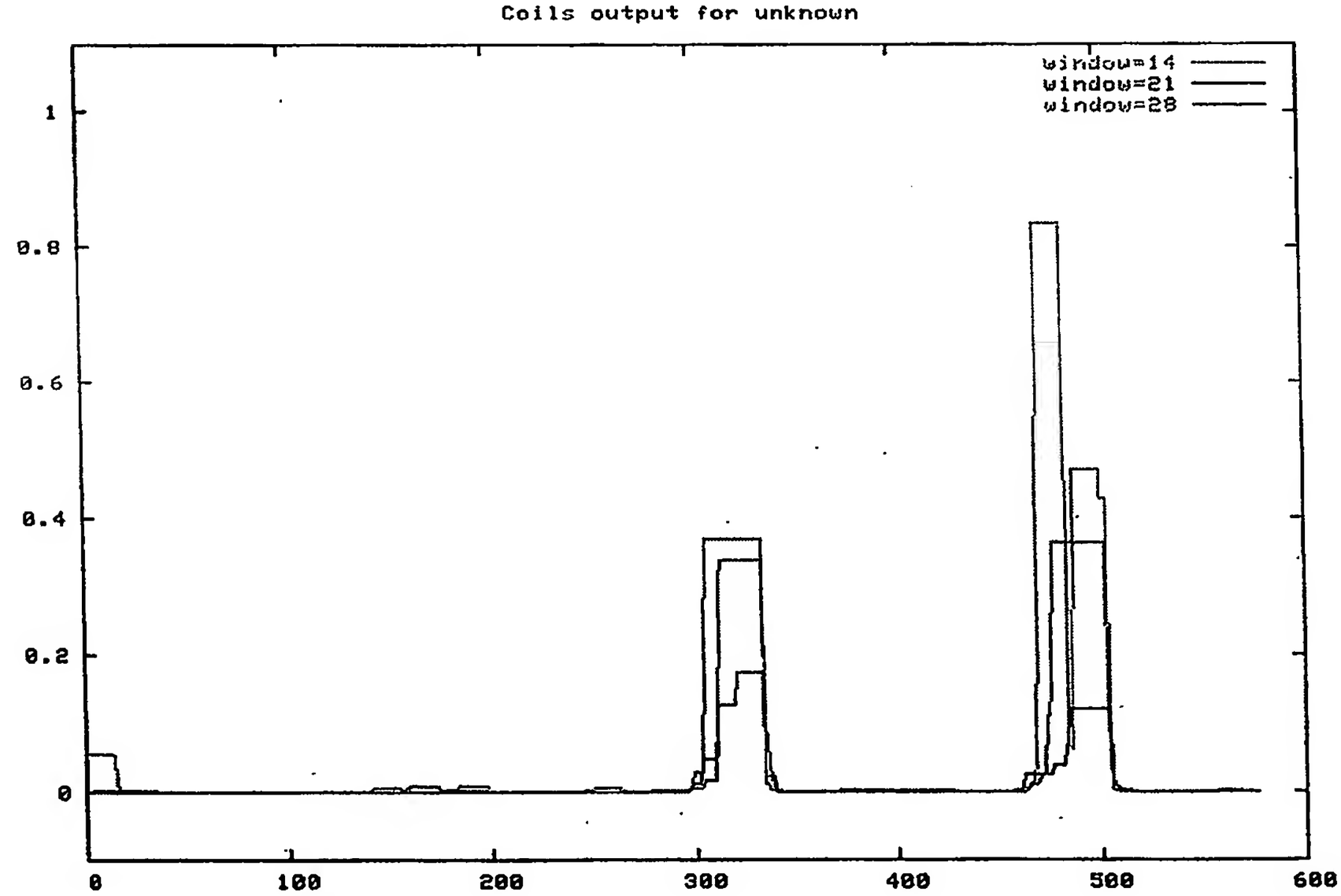

FIGURE 9

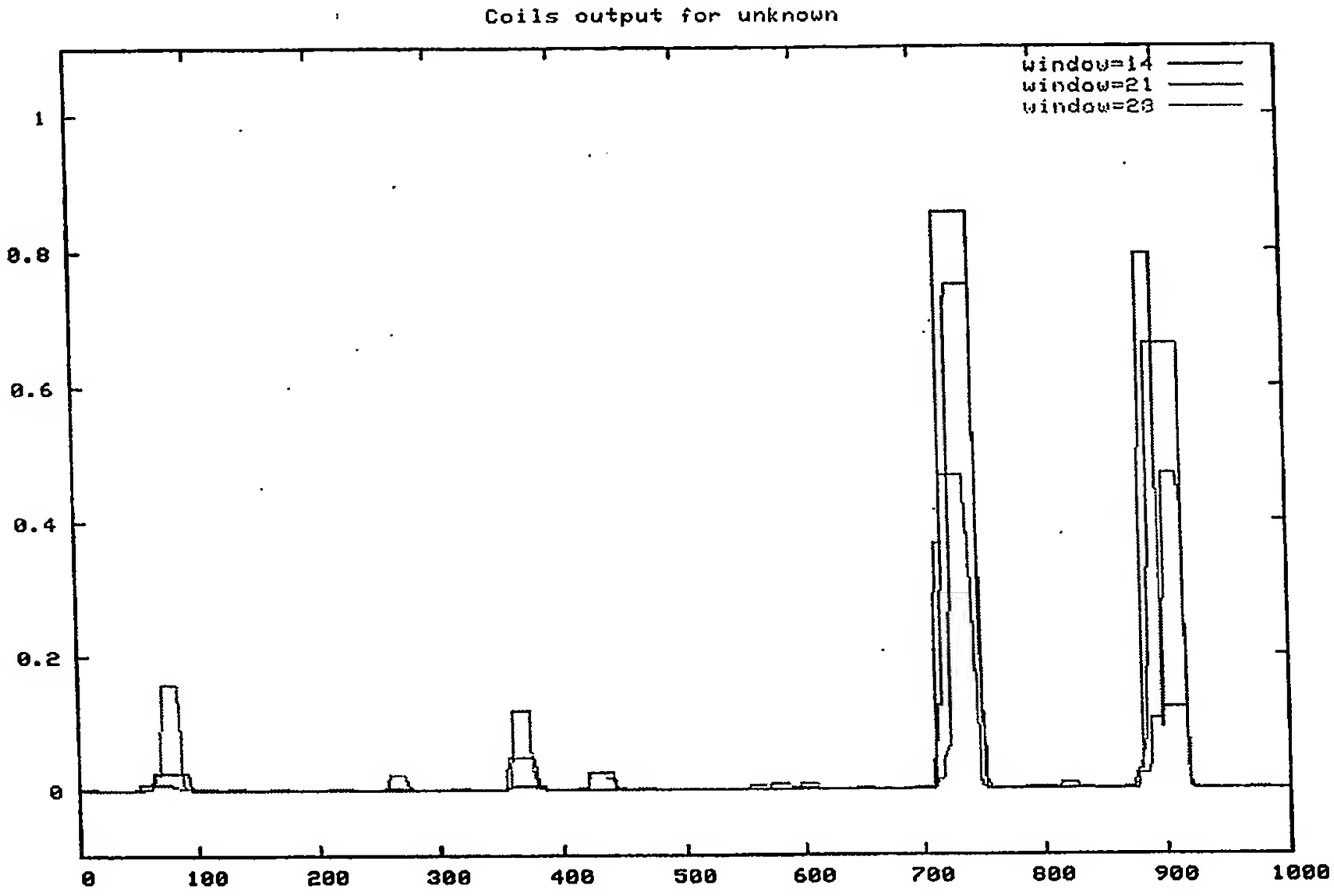

FIGURE 10

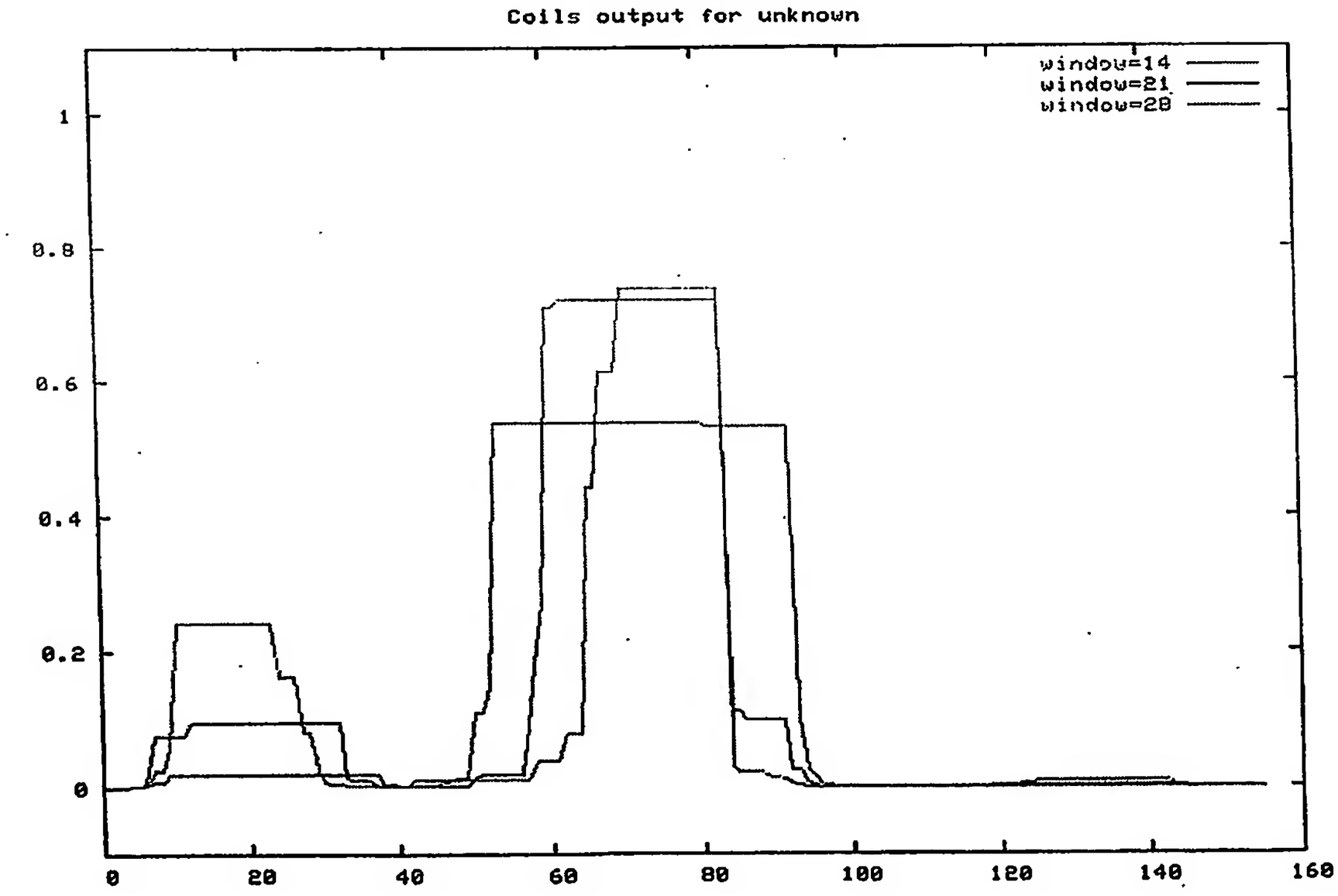

FIGURE 11

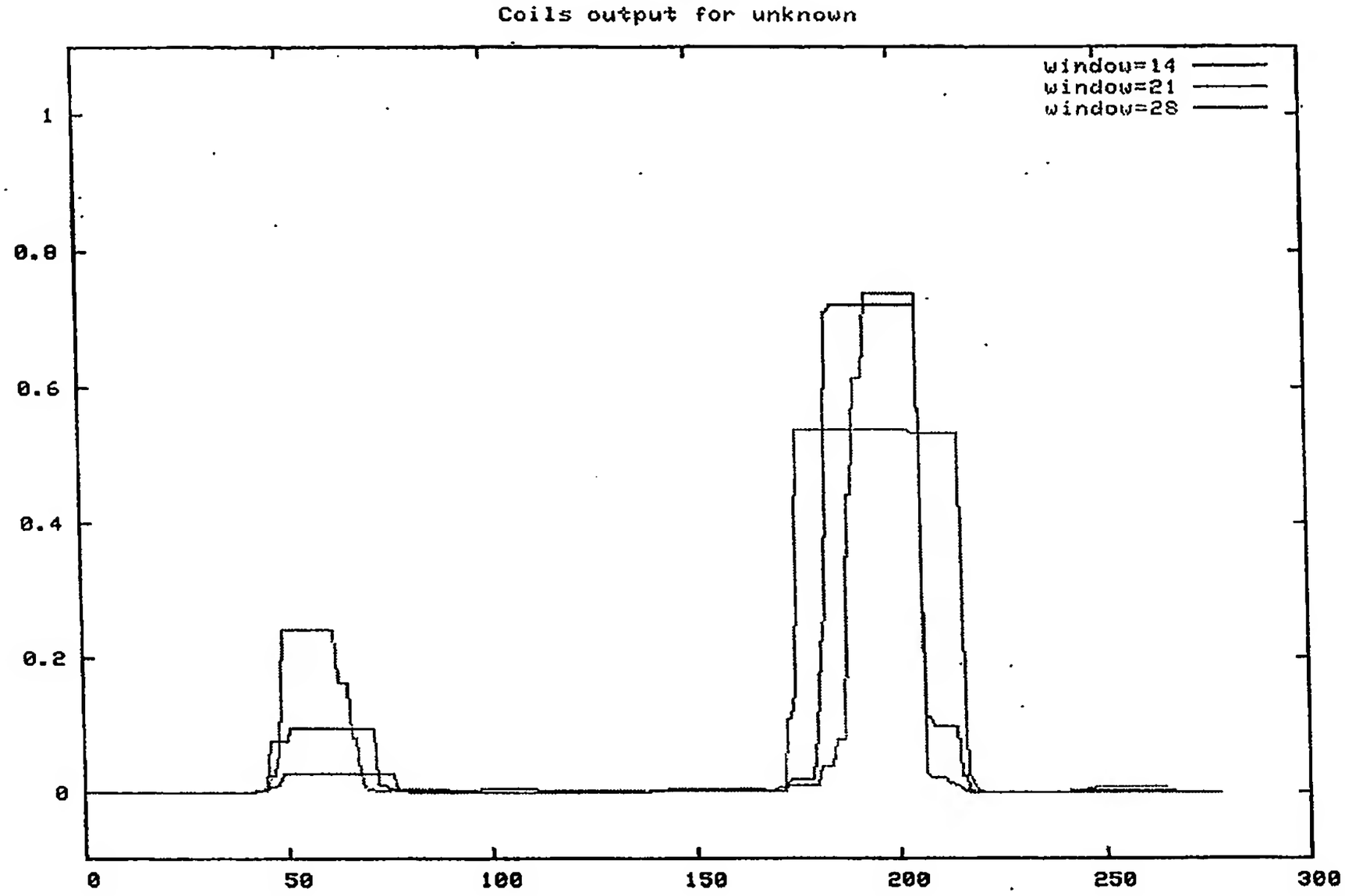

FIGURE 12

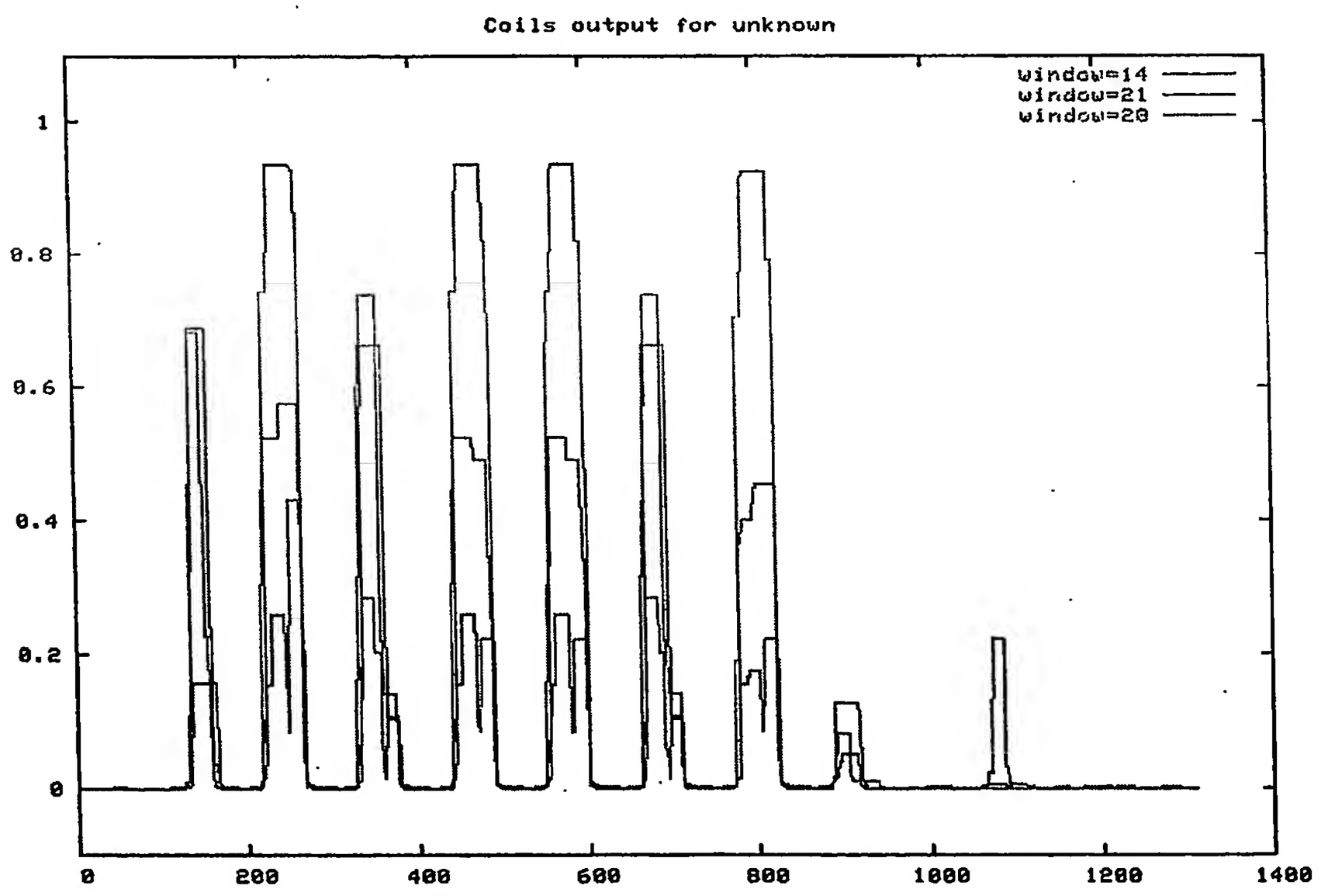

FIGURE 13

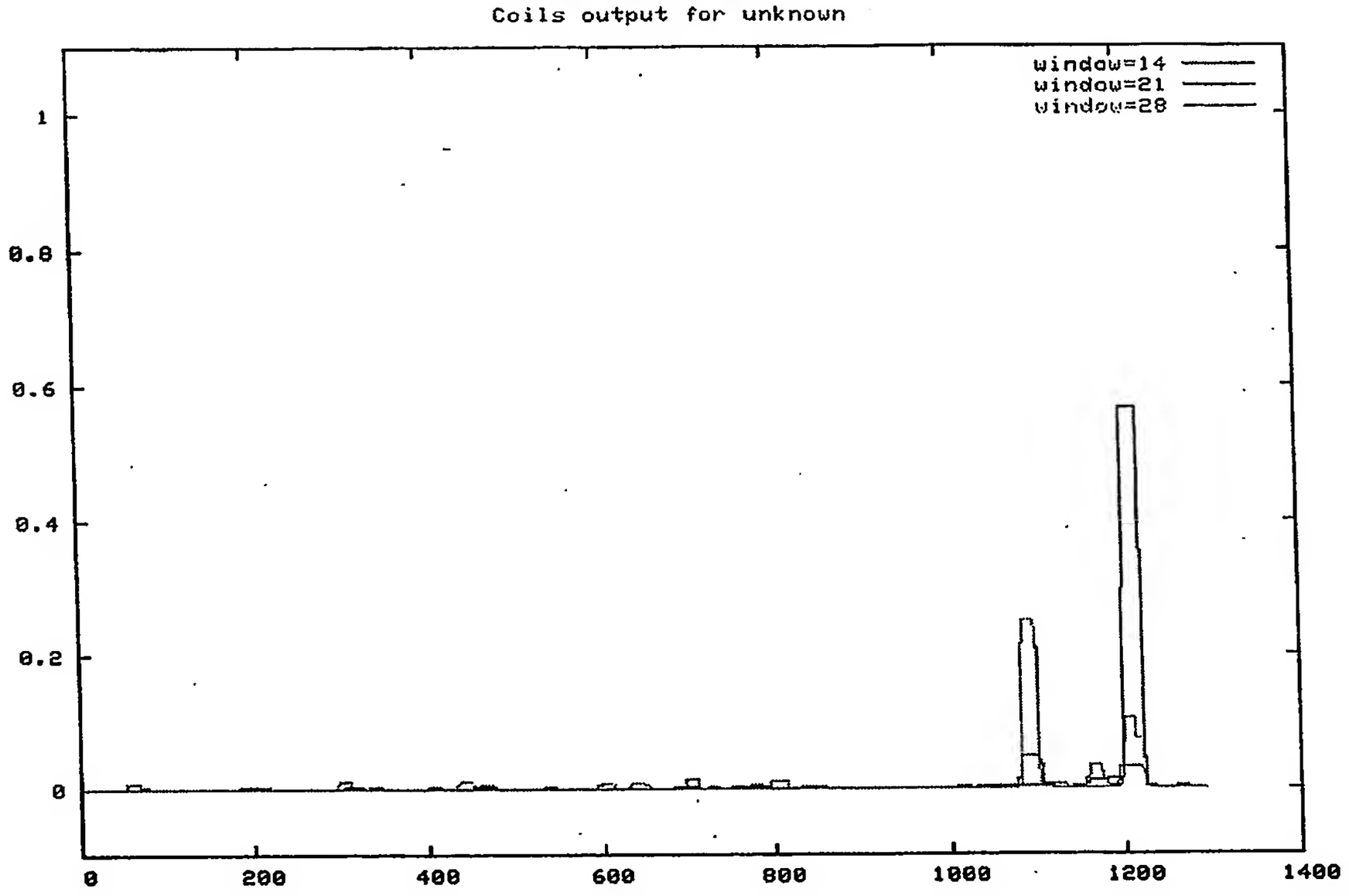

FIGURE 14

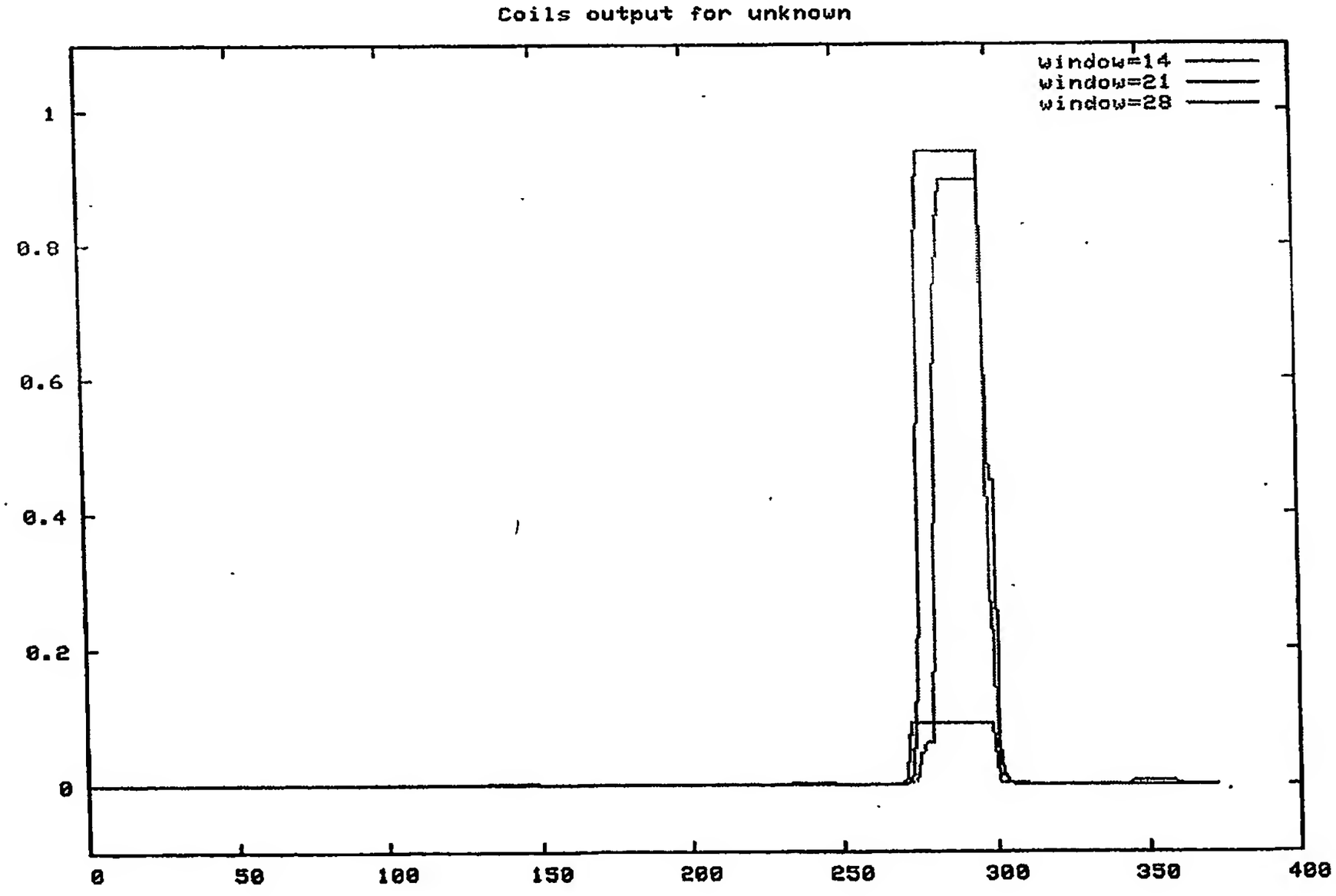

FIGURE 15

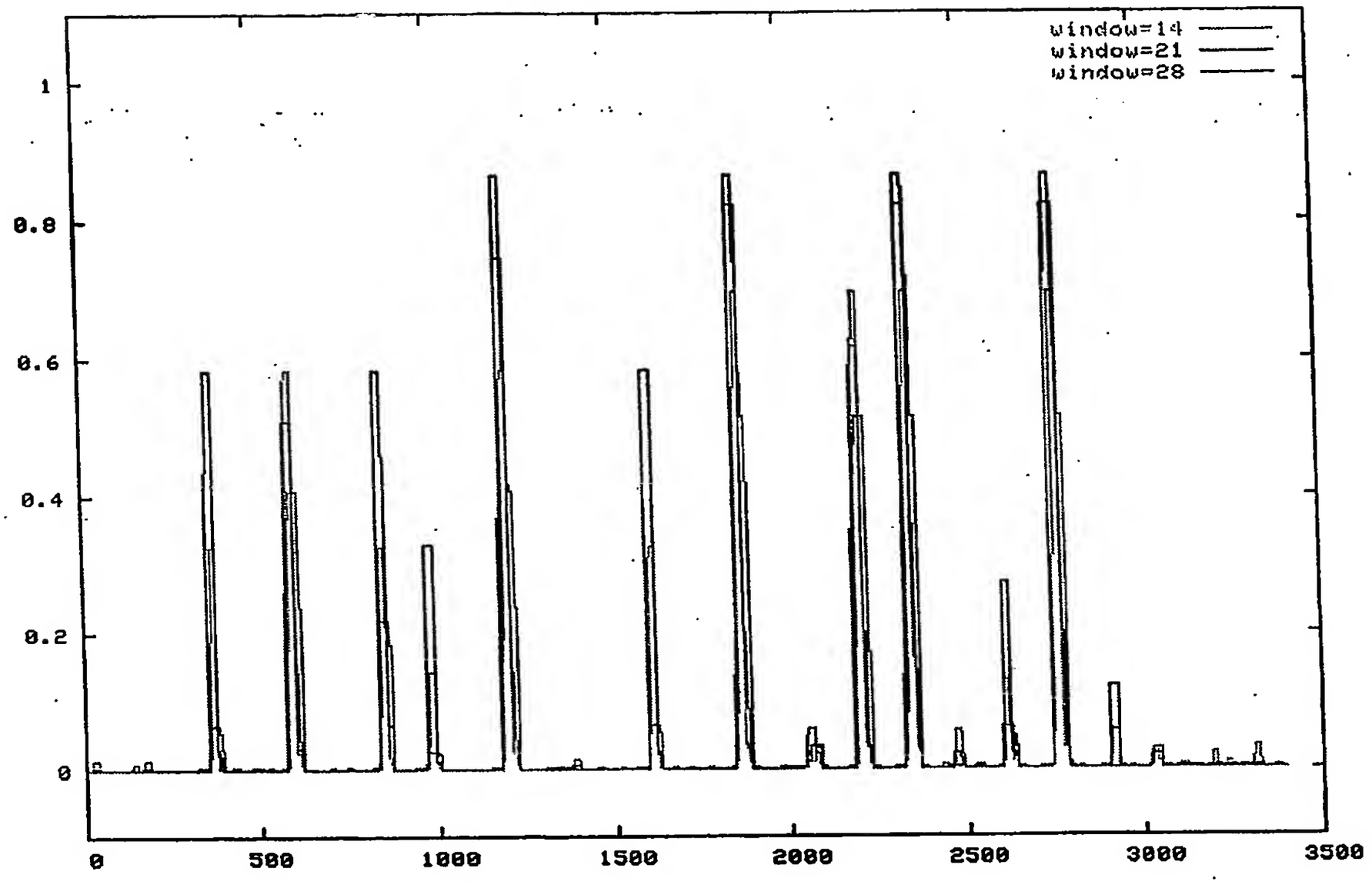

FIGURE 16

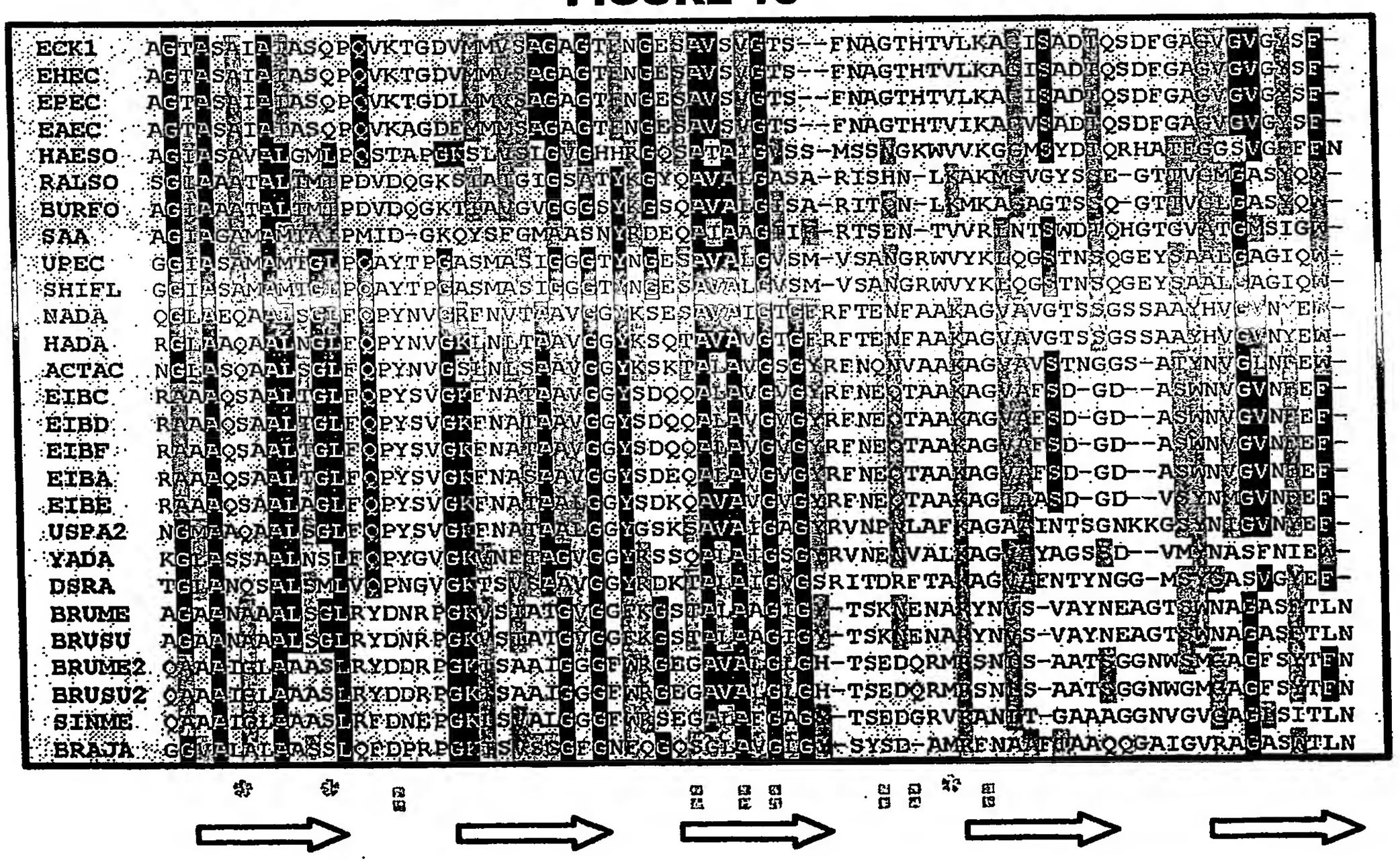

FIGURE 17

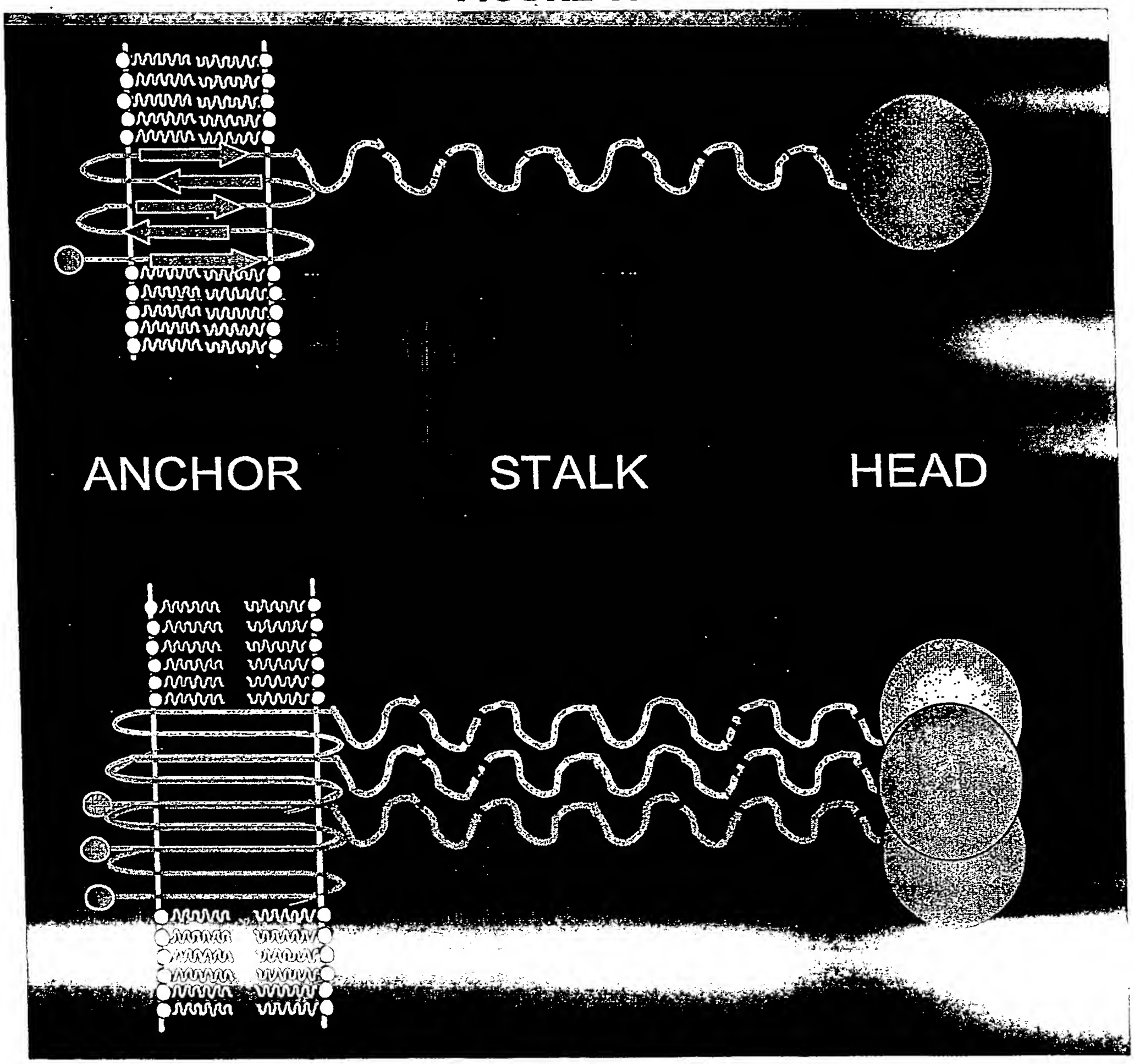

FIGURE 20

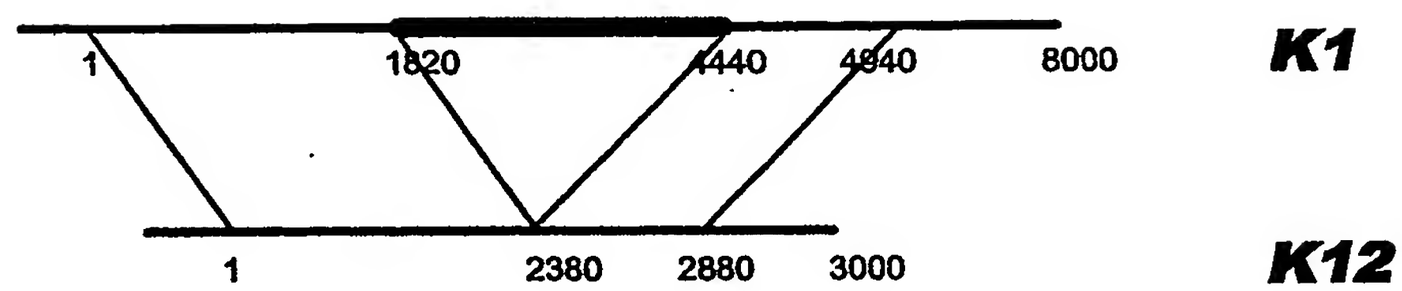

FIGURE 18

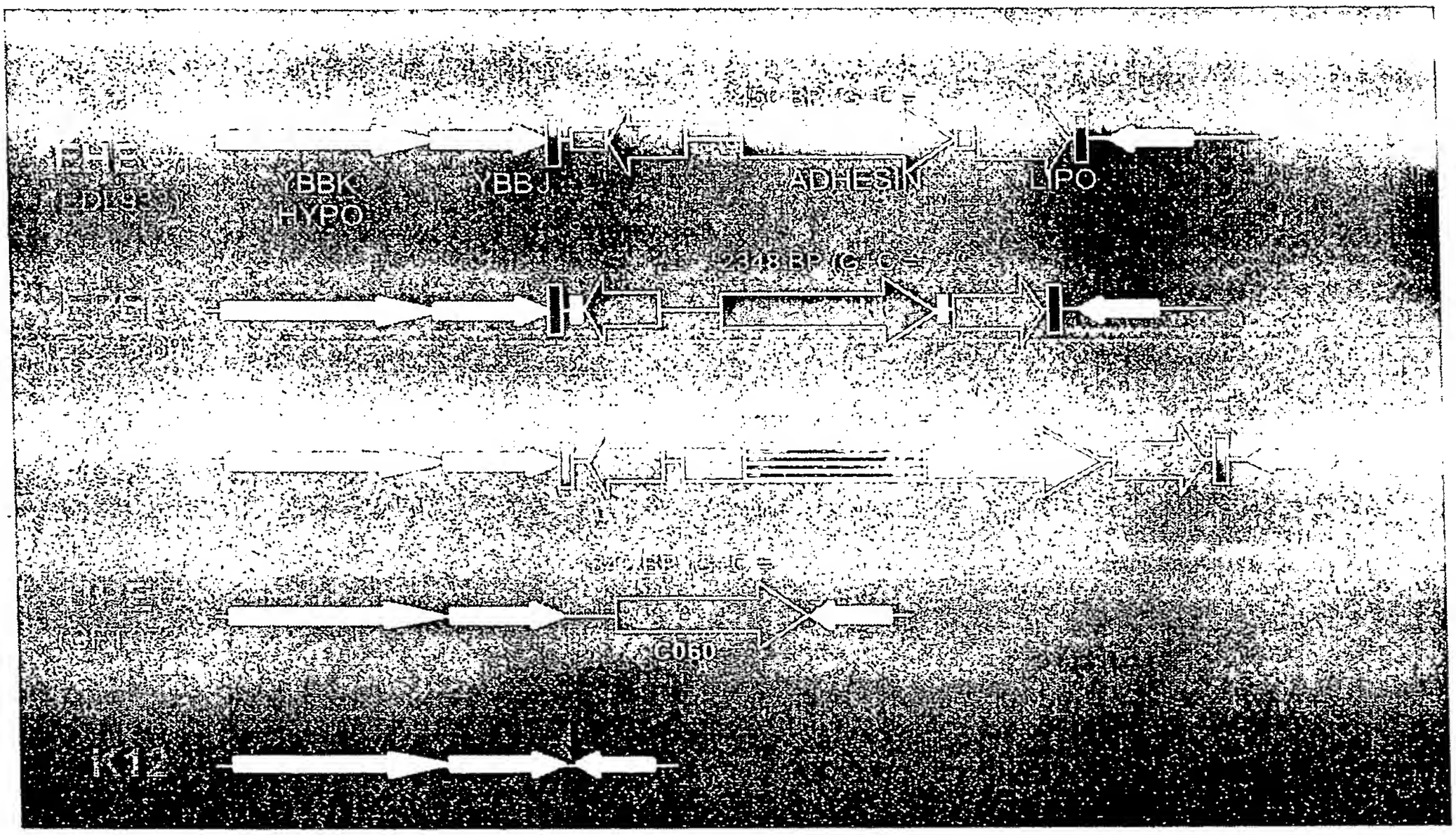

FIGURE 19